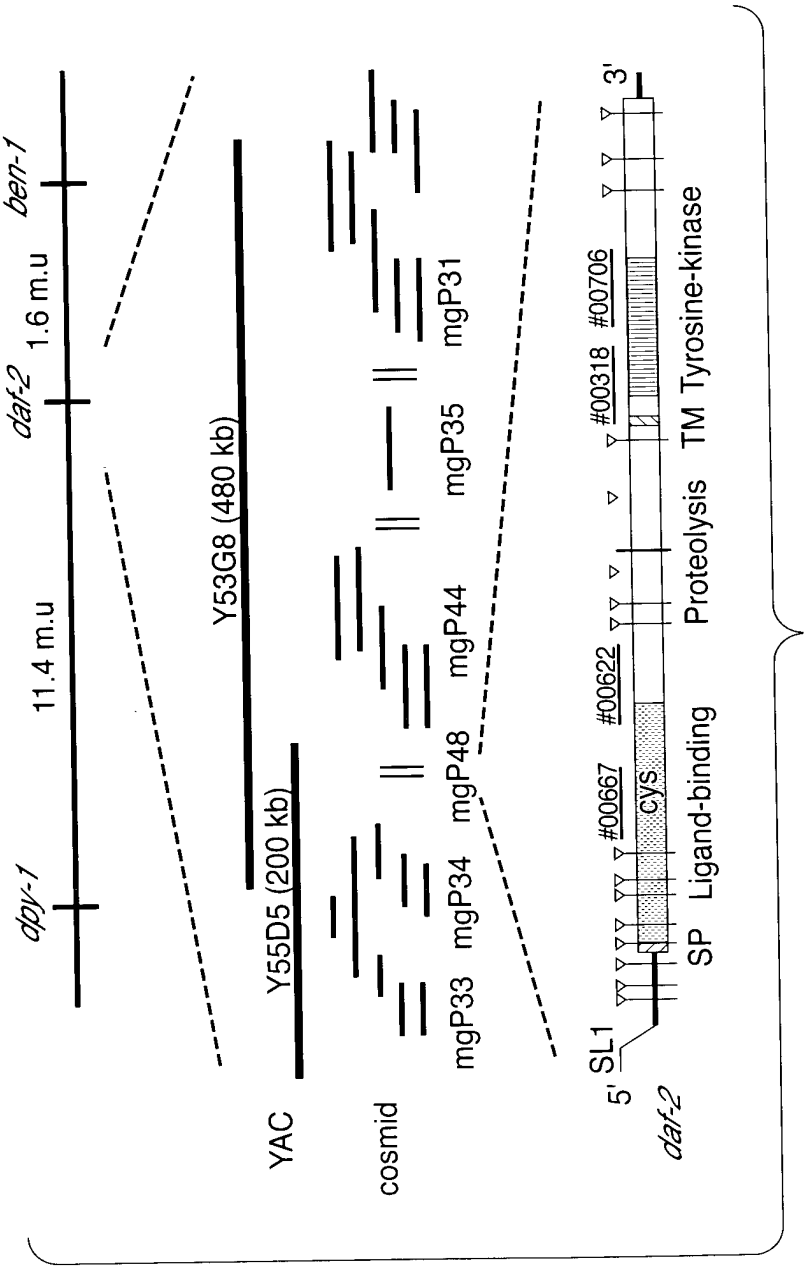

Fig. 1

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 181 HLITSSINDVVVDNAAEYAVTETGLMCPRGACEEDKGESKCHYLEEKNQEQGVERVQSCW
 241 SNTTCQKSCAYDRLLPTKEIGPGCDANGDRCHDQCVGGCERVNDATACHACKNVYHKGKC
 301 IEKCDAHLYLLLQRRCVTREQCLQLNPVLSNKTVPIKATAGLCSDKCPDGYQINPDDHRE
 361 CRKCVGKCEIVCEINHVIDTFPKAQAIRLCNIIDGNLTIEIRGKQDSGMASELKDIFANI
 421 HTITGYLLVRQSSPFISLNMFRNLRRIEAKSLFRNLYAITVFENPNLKKLFDSTTDLTLD
 481 RGTVSIANNKMLCFKYIKQLMSKLNIPLDPIDQSEGTNGEKAICEDMAINVSITAVNADS
 541 VFFSWPSFNITDIDQRKFLGYELFFKEVPRIDENMTIEEDRSACVDSWQSVFKQYYETSN
 601 GEPTPDIFMDIGPRERIRPNTLYAYYVATQMVLHAGAKNGVSKIGFVRTSYYTPDPPTLA
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 781 PMSAIESSAFENKLLDEVLMPRDTMRVRRSIEDANRVSEELEKAENLGKAPKTLGGKKPL
 841 IHISKKKPSSSSTTSTPAPTIASMYALTRKPTTVPGTRIRLYEIYEPLPGSWAINVSALA
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 961 WRFMNNSQQVNVTWDPPTEVNGGIFGYVVKLKSKVDGSIVMTRCVGAKRGYSTRNQGVLF
1021 QNLADGRYFVSVTATSVHGAGPEAESSDPIVVMTPGFFTVEIILGMLLVFLILMSIAGCI
1081 IYYYIQVRYGKKVKALSDFMQLNPEYCVDNKYNADDWELRQDDVVLGQQCGEGSFGKVYL
1141 GTGNNVVSLMGDRFGPCAIKINVDDPASTENLNYLMEANIMKNFKTNFIVQLYGVISTVQ
1201 PAMVVMEMMDLGNLRDYLRSKREDEVFNETDCNFFDIIPRDKFHEWAAQICDGMAYLESL
1261 KFCHRDLAARNCMINRDETVKIGDFGMARDLFYHDYYKKPSGKRMMPVRWMSPESLKDGKF
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1381 WRYSPRDRPTFLQLVHLLAAEASPEFRDLSFVLTDNQMILDDSEALDLDDIDDTDMNDQV
1441 VEVAPDVENVEVQSDSERRNTDSIPLKQFKTIPPINATTSHSTISIDETPMKAKQREGSL
1501 DEEYALMNHSGGPSDAEVRTYAGDGDYVERDVRENDVPTRRNTGASTSSYTGGGPYCLTN
1561 RGGSNERGAGFGEAVRLTDGVGSGHLNDDDYVEKEISSMDTRRSTGASSSSYGVPQTNWS
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Fig. 2A

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 151  agacgacaca aaatttgga aaatttggaa gaagagaatc tcggcccgag
 201  ctgctcgtcg acgacttcaa caaccgctgc caccgaagct ctcggaacaa
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 501  cttttactgc tattcgcttt tgtacagccg tgtgcctcaa tagtcgaaaa
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2651  gacgattgta gccgataagc cagtcgatat tccgtcatca cgtaccgtag
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Fig. 2B-1

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2851  catttgagaa taagctgttg gatgaggttt taatgccgag agacacgatg
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3001  cgctgatcca tatttcgaag aagaagccgt cgagcagcag caccacatcc
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Fig. 2B-2

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5701  cccacattat catatctcta cacgaatatc ggatttttt tcagattttt
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Fig. 2B-3

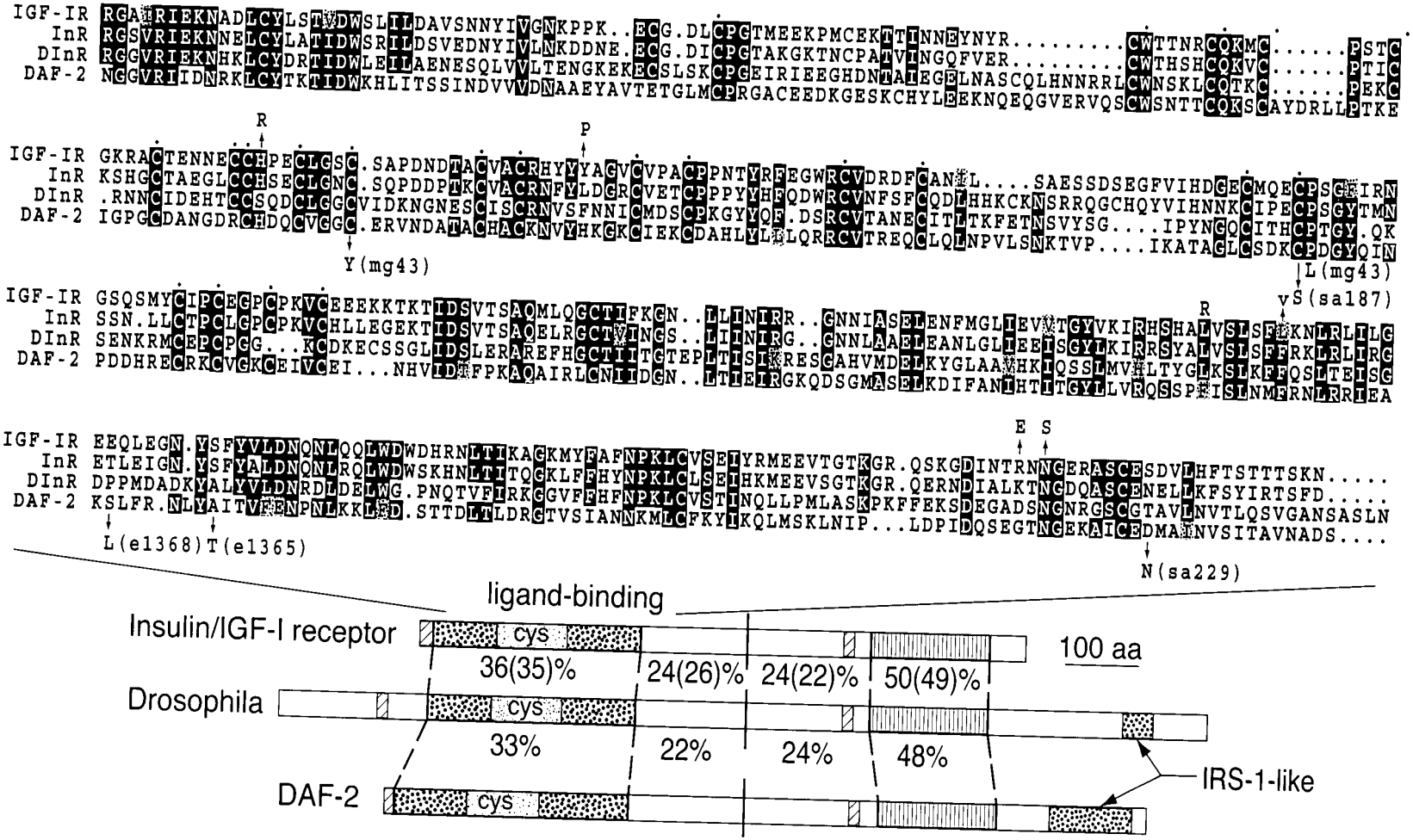

Fig. 2C-1

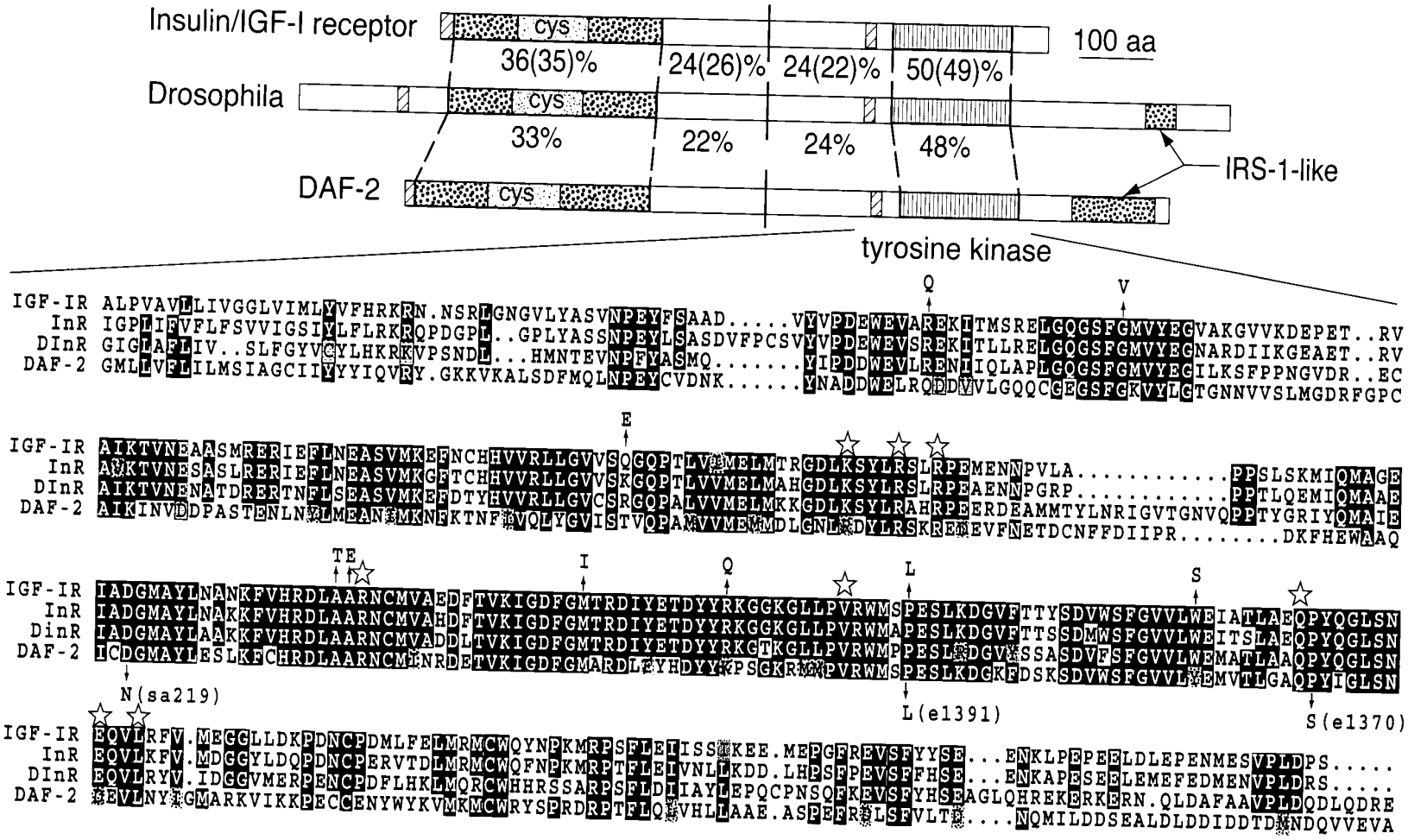

Fig. 2C-2

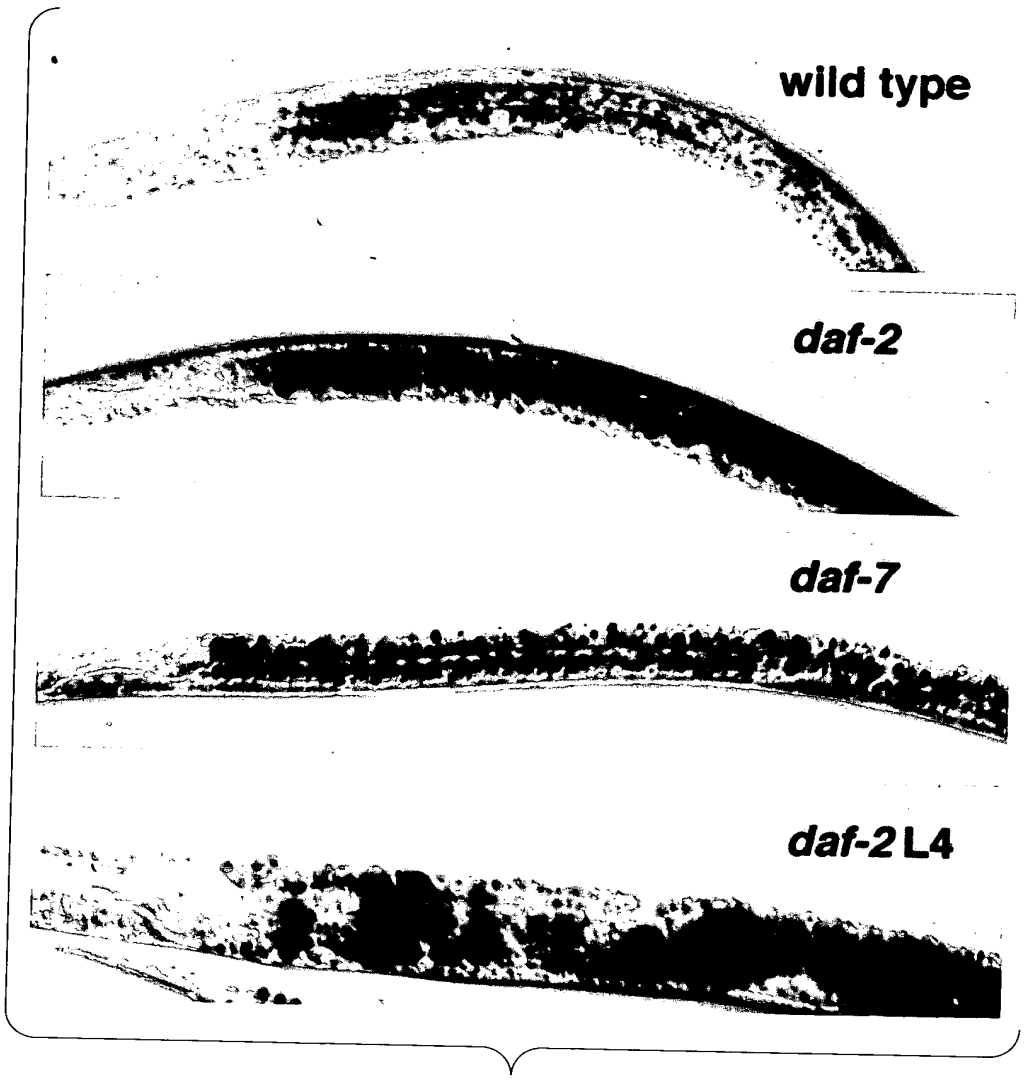

Fig. 3

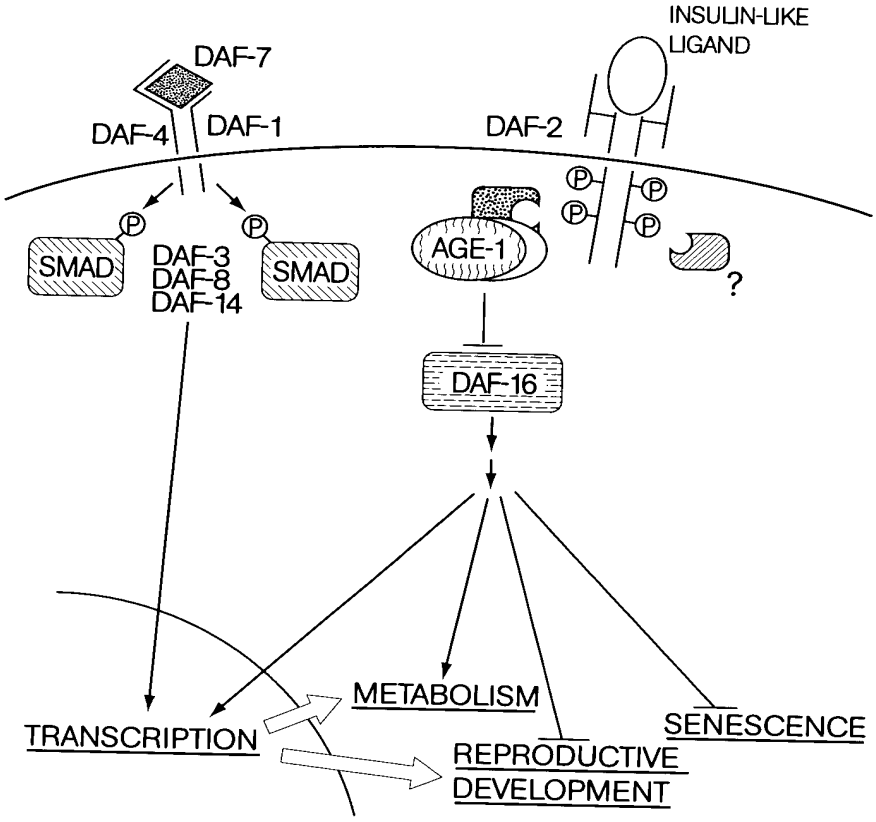

Fig. 4

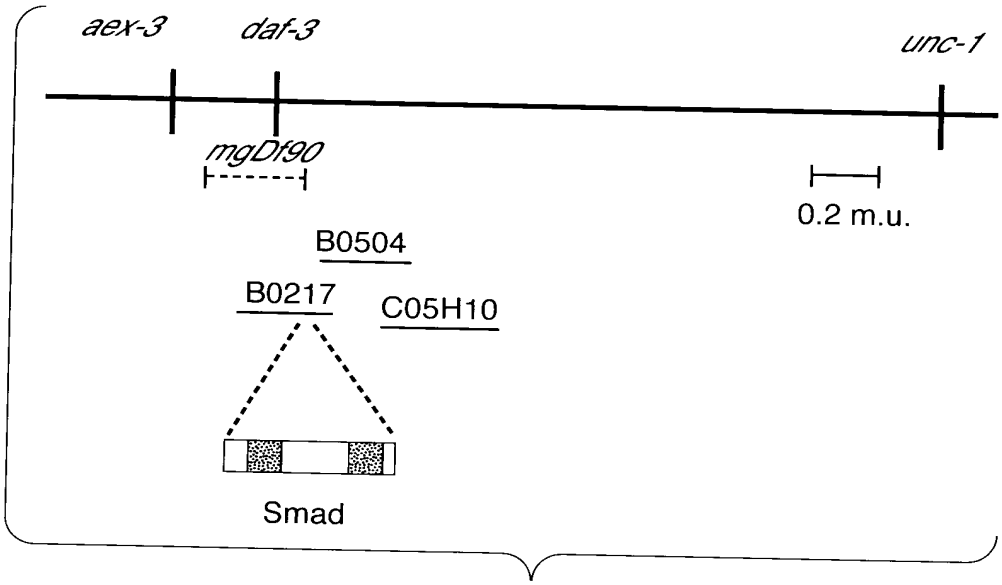

Fig. 5A

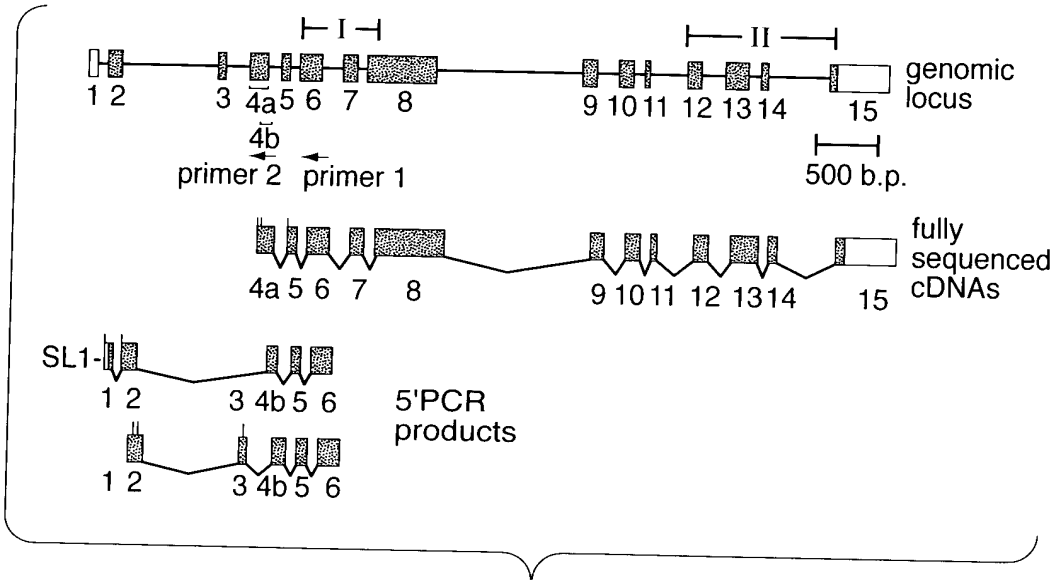

Fig. 5B

Domain I

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             mg125 P->L
         RLQVHGRKGFPHVVYGKLWRFNEMTKNETRHVDHCKHAFEMKSDMVCVNPYH
         RLQVAGRKGFPHVIYARLWRWPDLHKNELKHVKYCQYAFDLKCDSVCVNPYH
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Domain II

```
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        mg132  G->E
         RKAIVDGIRFSYKKDGSVWLQNRMKYPVFVTSGYLDEQSGGLKKDKVHKVYGCA
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Fig. 5C

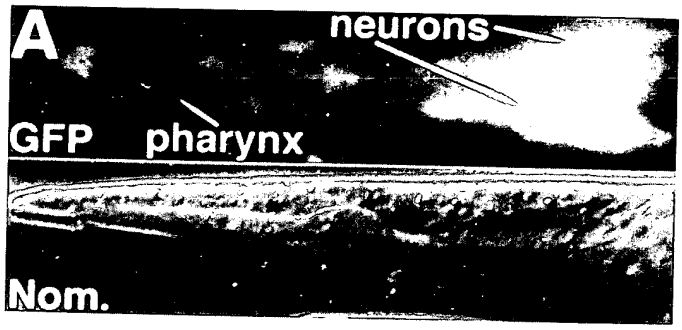

Fig. 6A

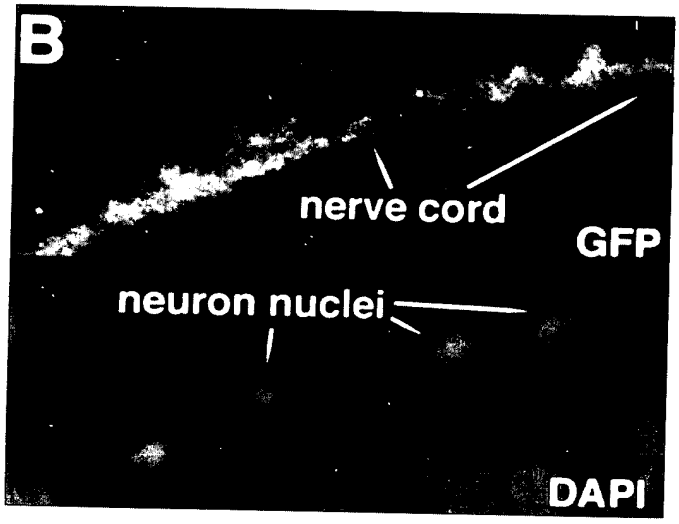

Fig. 6B

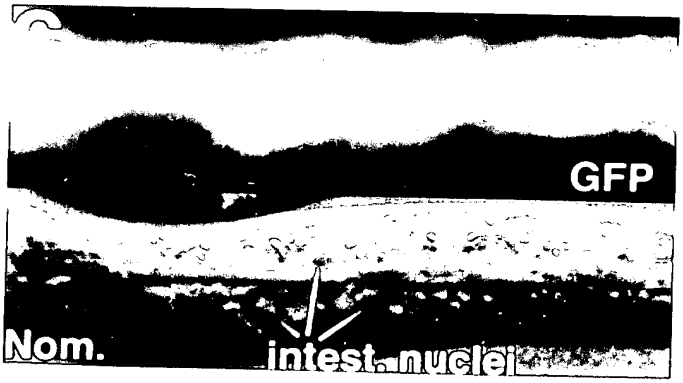

Fig. 6C

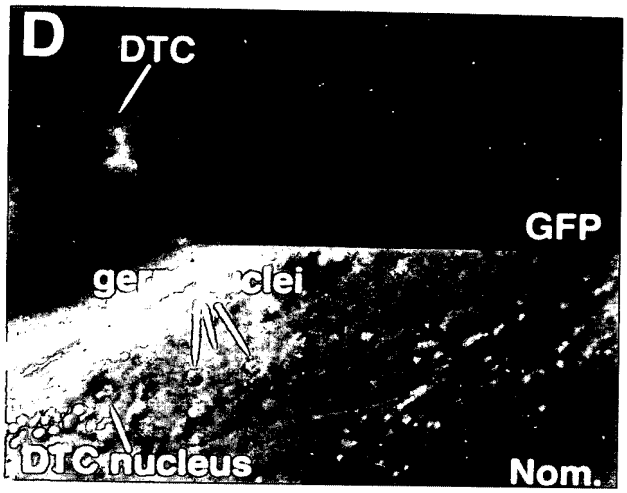

Fig. 6D

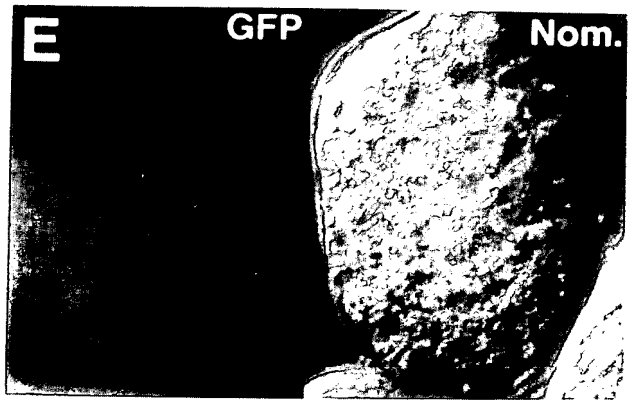

Fig. 6E

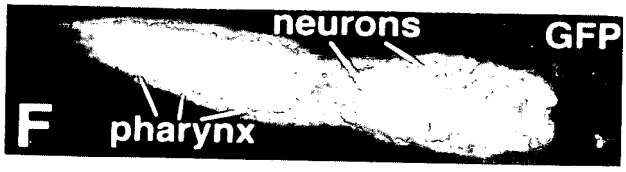

Fig. 6F

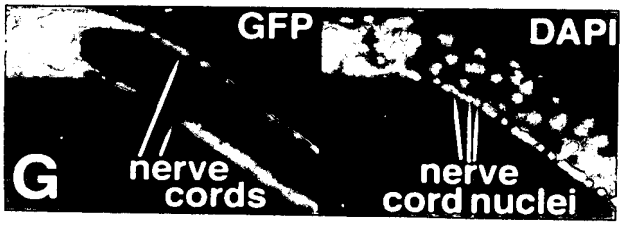

Fig. 6G

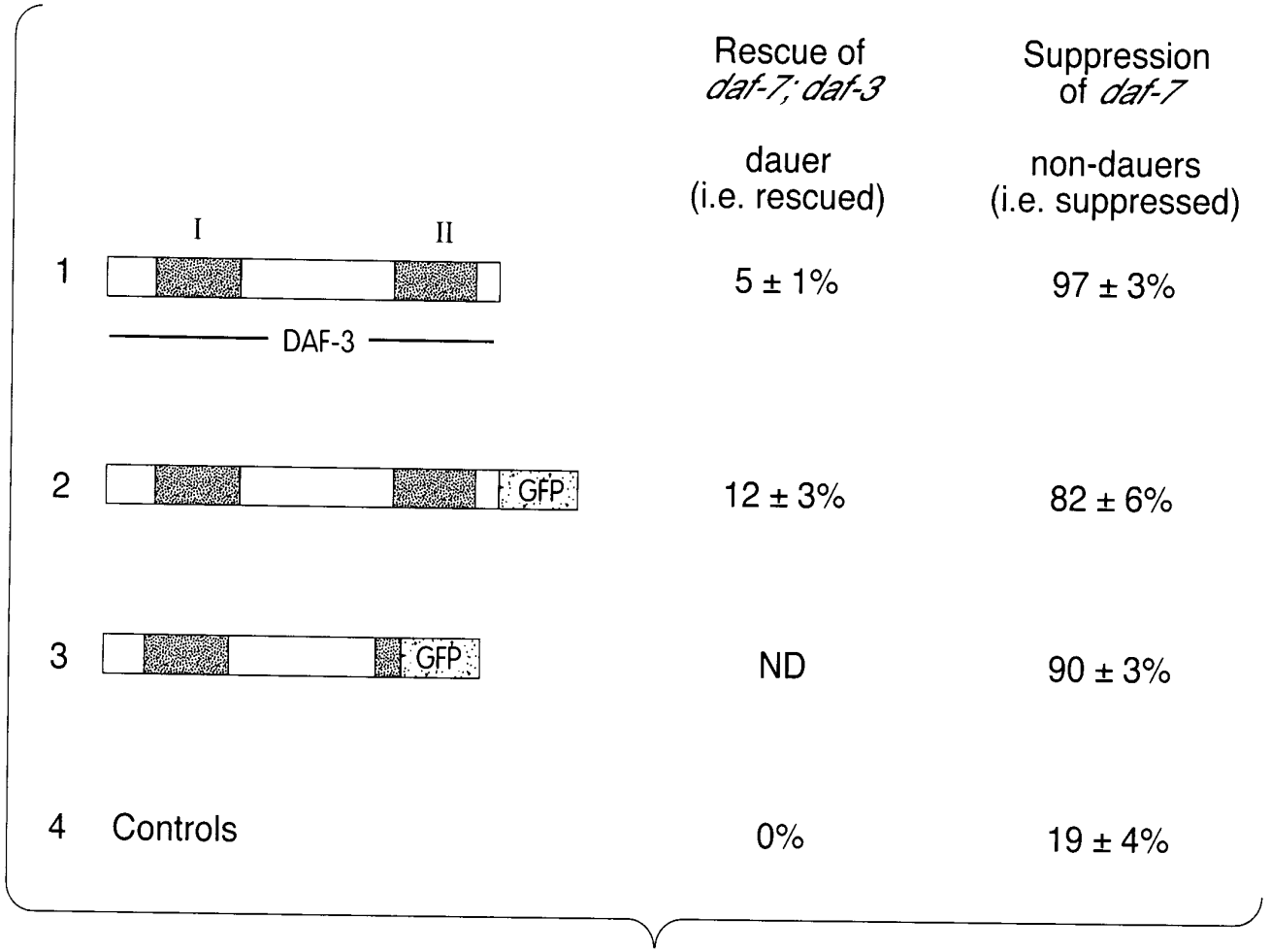

Fig. 7

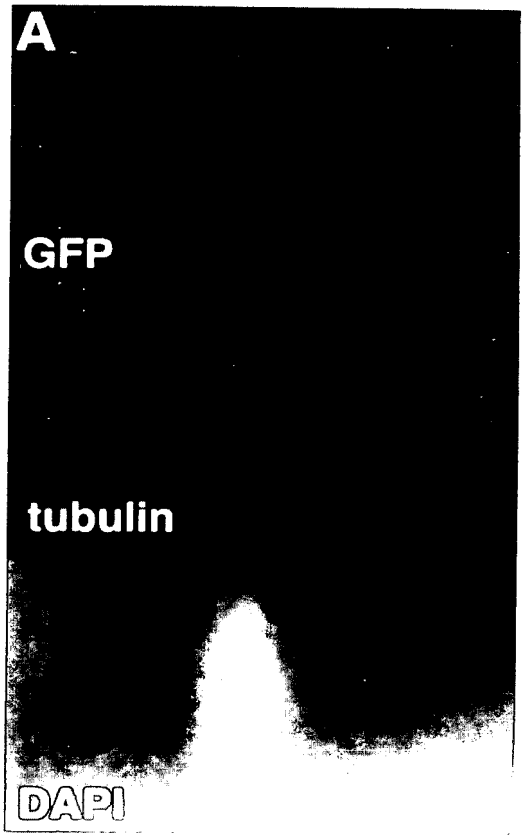

Fig. 8A

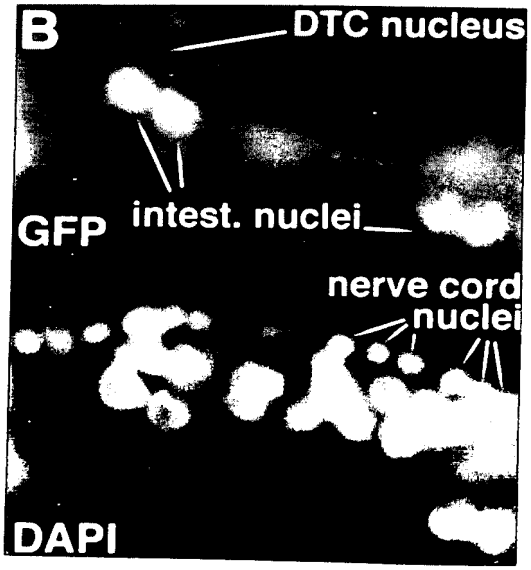

Fig. 8B

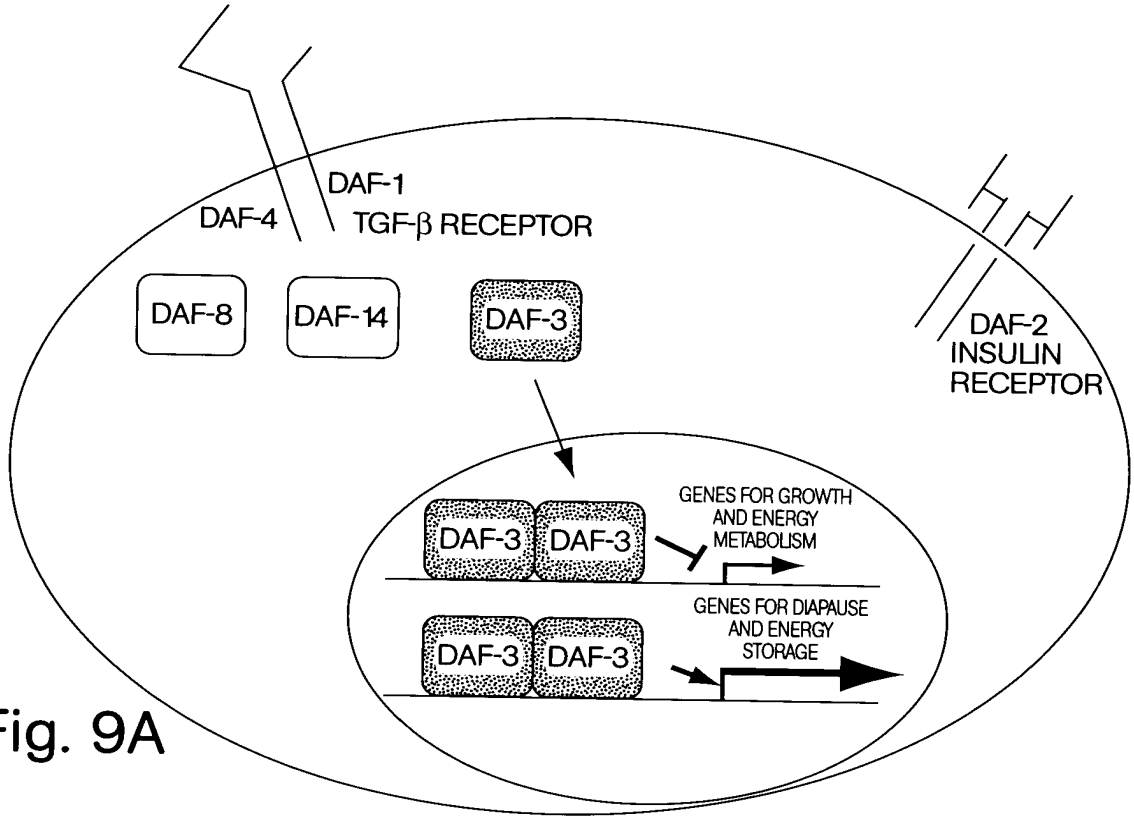

Fig. 9A

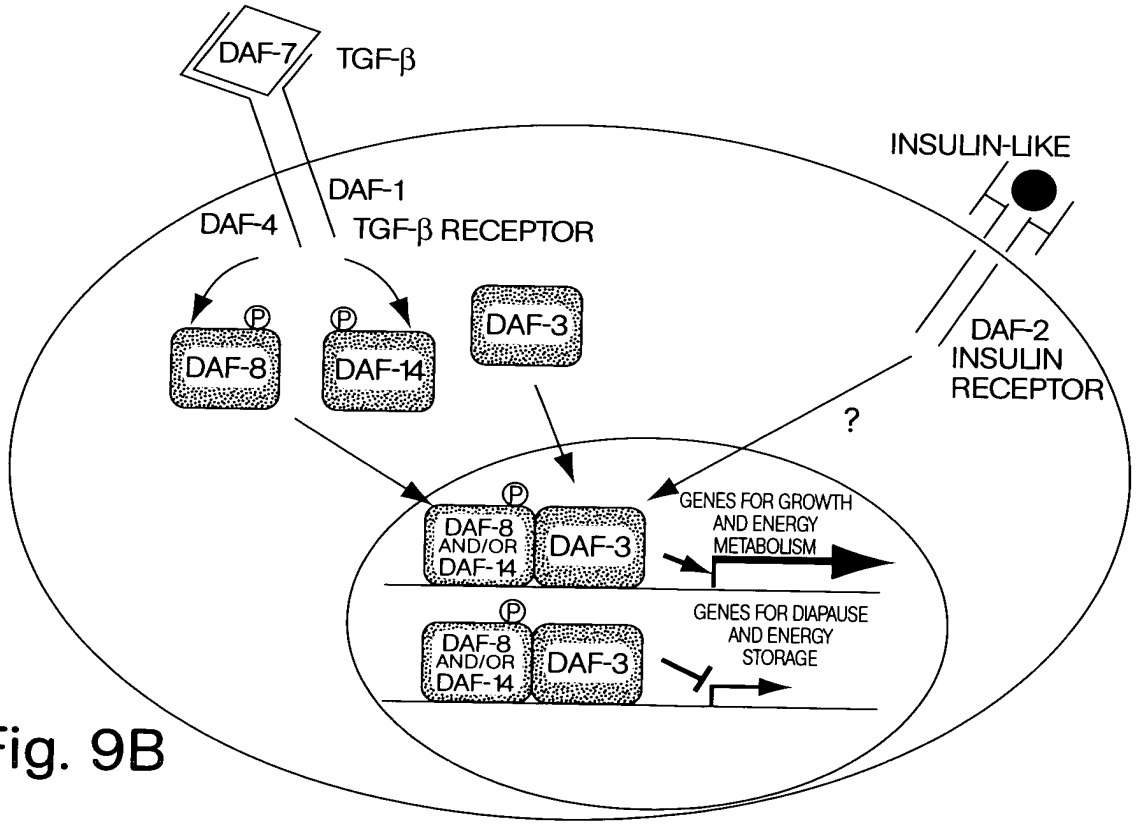

Fig. 9B

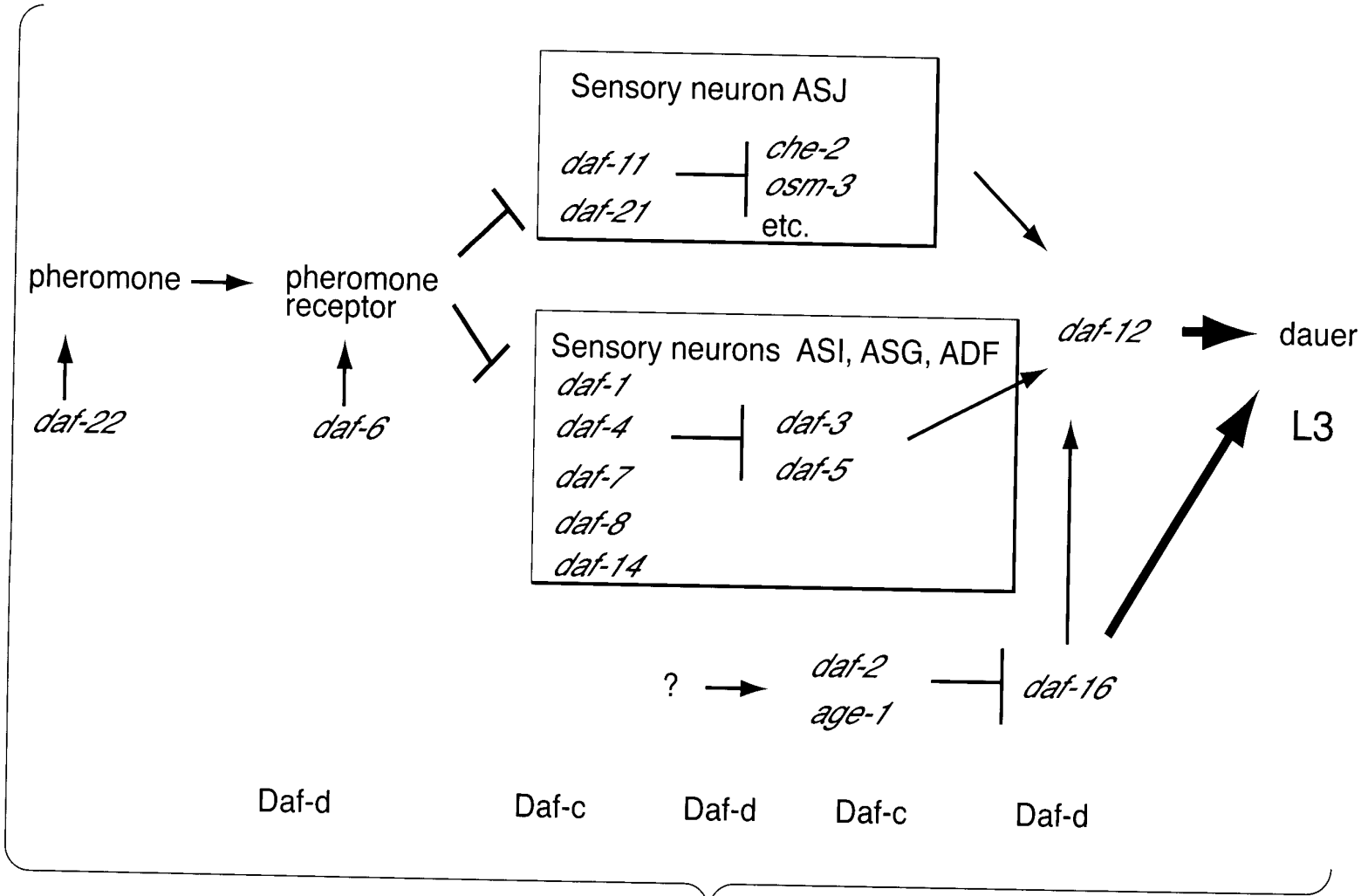

Fig. 10

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 151  gaagatggtg tcaactaccc ggatccagat ttatttgaca caaaaaacac
 201  aaatatgacc gagtacgatt tggatgtgtt gaagcttgga aaaccagcag
 251  tagatgaagc acggaaaaag atcgaagttc ccgacgctag tgcgccgcca
 301  aacaaaattg tagaatattt gatgtattat agaacgttaa aagaaagtga
 351  actcatacaa ctgaatgcgt atcggacaaa acgaaatcga ttatcgttga
 401  acttggtcaa aaacaatatt gatcgagagt tcgaccaaaa agcttgcgag
 451  tccctggtga aaaaattgaa ggataagaag aatgatctcc agaacctgat
 501  tgatgtggtt ctttcaaaag gtacaaaata taccggttgc attacaattc
 551  caaggacact tgatggccgg ttacaggtcc acggaagaaa aggtttccct
 601  cacgtagtct atggcaaact gtggaggttt aatgaaatga caaaaaacga
 651  aacgcgtcat gtggaccact gcaagcacgc atttgaaatg aaaagtgaca
 701  tggtatgcgt gaatccctat cactacgaaa ttgtcattgg aactatgatt
 751  gttgggcaga gggatcatga caatcgagat atgccgccgc cacatcaacg
 801  ctaccacact ccaggtcggc aggatccagt tgacgatatg agtagattta
 851  taccaccagc ttccattcgt ccgcctccga tgaacatgca cacaaggcct
 901  cagcctatgc ctcaacaatt gccttcagtt ggcgcaacgt ttgcccatcc
 951  tctcccacat caggcgccac ataacccagg ggtttcacat ccgtactcca
1001  ttgctccaca gacccattac ccgttgaaca tgaacccaat tccgcaaatg
1051  ccgcaaatgc cacaaatgcc accacctctc catcagggat atggaatgaa
1101  tgggccgagt tgctcttcag aaaacaacaa tccattccac caaaatcacc
1151  attataatga tattagccat ccaaatcact attcctacga ctgtggtccg
1201  aacttgtacg ggtttccaac tccttatccg gattttcacc atcctttcaa
1251  tcagcaacca caccagccgc cacaactatc acaaaaccat acgtcccaac
1301  aaggcagtca tcaaccaggg caccaaggtc aggtaccgaa tgatccacca
1351  atttcaagac cagtgttaca accatcaaca gtcaccttgg acgtgttccg
1401  tcggtactgt agacagacat ttggaaatcg atttttgaa ggagaaagtg
1451  aacaatccgg cgcaataatt cggtctagta acaaattcat tgaagaattt
1501  gattcgccga tttgtggtgt gacagttgtt cgaccgcgga tgacagacgg
1551  tgaggttttg gagaacatca tgccggaaga tgcaccatat catgacattt
1601  gcaagttcat tttgaggctc acatcagaaa gtgtaacttt ctcaggagag
1651  gggccagaag ttagtgattt gaacgaaaaa tggggaacaa ttgtgtacta
1701  tgagaaaaat ttgcaaattg gcgagaaaaa atgttcgaga ggaaatttcc
1751  acgtggatgg cggattcatt tgctctgaga atcgttacag tctcggactt
1801  gagccaaatc caattagaga accagtggcg tttaaagttc gtaaagcaat
1851  agtggatgga attcgctttt cctacaaaaa agacgggagt gtttggcttc
1901  aaaaccgcat gaagtacccg gtatttgtca cttctgggta tctcgacgag
1951  caatcaggag gcctaaagaa ggataaagtg cacaaagttt acggatgtgc
2001  gtctatcaaa acgtttggct tcaacgtttc caaacaaatc atcagagacg
2051  cgcttctttc caagcaaatg gcaacaatgt acttgcaagg aaaattgact
```

Fig. 11A-1

```
2101  ccgatgaatt atatctacga gaagaagact caggaagagc tgcgaaggga
2151  agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct
2201  cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat
2251  gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat
2301  ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg
2351  aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact
2401  tttttcactc accctactag atactgattt agtcttattc caaatcatcc
2451  aacgatatca aacttttttcc tttgaacttt gcatactatg ttatcacaag
2501  ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa
2551  gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac
2601  aatgtatccc atacctcaat ctttaatagt catcagtcac tggtcccgca
2651  ccaatttttt cgattcgcat atgtcatata ttgcaccgtg gccctttta
2701  ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa
2751  ccaccatttt gagtaataaa tgtatttttt gtgg
```

Fig. 11A-2

```
   1  gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
  51  ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gttcccgacg agcacacacc gatgatgtca ccagtgaata
 301  caactacaaa gattctacaa cggagtggta ttaaaatgga aatcccgcca
 351  tatttggatc cagacagtca ggatgatgac ccggaagatg gtgtcaacta
 401  cccggatcca gatttatttg acacaaaaaa cacaaatatg accgagtacg
 451  atttggatgt gttgaagctt ggaaaaccag cagtagatga agcacggaaa
 501  aagatcgaag ttcccgacgc tagtgcgccg ccaaacaaaa ttgtagaata
 551  tttgatgtat tatagaacgt taaaagaaag tgaactcata caactgaatg
 601  cgtatcggac aaaacgaaat cgattatcgt tgaacttggt caaaaacaat
 651  attgatcgag agttcgacca aaaagcttgc gagtccctgg tgaaaaaatt
 701  gaaggataag aagaatgatc tccagaacct gattgatgtg gttctttcaa
 751  aaggtacaaa atataccggt tgcattacaa ttccaaggac acttgatggc
 801  cggttacagg tccacggaag aaaaggtttc cctcacgtag tctatggcaa
 851  actgtggagg tttaatgaaa tgacaaaaaa cgaaacgcgt catgtggacc
 901  actgcaagca cgcatttgaa atgaaaagtg acatggtatg cgtgaatccc
 951  tatcactacg aaattgtcat tggaactatg attgttgggc agagggatca
1001  tgacaatcga gatatgccgc cgccacatca acgctaccac actccaggtc
1051  ggcaggatcc agttgacgat atgagtagat ttataccacc agcttccatt
1101  cgtccgcctc cgatgaacat gcacacaagg cctcagccta tgcctcaaca
1151  attgccttca gttggcgcaa cgtttgccca tcctctccca catcaggcgc
1201  cacataaccc aggggtttca catccgtact ccattgctcc acagacccat
1251  tacccgttga acatgaaccc aattccgcaa atgccgcaaa tgccacaaat
1301  gccaccacct ctccatcagg gatatggaat gaatgggccg agttgctctt
1351  cagaaaacaa caatccattc caccaaaatc accattataa tgatattagc
1401  catccaaatc actattccta cgactgtggt ccgaacttgt acgggtttcc
1451  aactccttat ccggattttc accatccttt caatcagcaa ccacaccagc
1501  cgccacaact atcacaaaac catacgtccc aacaaggcag tcatcaacca
1551  gggcaccaag gtcaggtacc gaatgatcca ccaatttcaa gaccagtgtt
1601  acaaccatca acagtcacct tggacgtgtt ccgtcggtac tgtagacaga
1651  catttggaaa tcgatttttt gaaggagaaa gtgaacaatc cggcgcaata
1701  attcggtcta gtaacaaatt cattgaagaa tttgattcgc cgatttgtgg
1751  tgtgacagtt gttcgaccgc ggatgacaga cggtgaggtt ttggagaaca
1801  tcatgccgga agatgcacca tatcatgaca tttgcaagtt cattttgagg
1851  ctcacatcag aaagtgtaac tttctcagga gaggggccag aagttagtga
1901  tttgaacgaa aaatggggaa caattgtgta ctatgagaaa aatttgcaaa
1951  ttggcgagaa aaaatgttcg agaggaaatt tccacgtgga tggcggattc
2001  atttgctctg agaatcgtta cagtctcgga cttgagccaa atccaattag
2051  agaaccagtg gcgtttaaag ttcgtaaagc aatagtggat ggaattcgct
```

Fig. 11B-1

```
2101  tttcctacaa aaaagacggg agtgtttggc ttcaaaaccg catgaagtac
2151  ccggtatttg tcacttctgg gtatctcgac gagcaatcag gaggcctaaa
2201  gaaggataaa gtgcacaaag tttacggatg tgcgtctatc aaaacgtttg
2251  gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa
2301  atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta
2351  cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg
2401  attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt
2451  ggagaagcat acccagaacg cccgtcaatt catgattgtc cagtttggat
2501  tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt
2551  acataaccaa ctgcttcgag ccgctaggaa tggaagattt tgcaaaattg
2601  ggaatcaacg tcagtgatga ctaaatgata actttttca ctcaccctac
2651  tagatactga tttagtctta ttccaaatca tccaacgata tcaaactttt
2701  tcctttgaac tttgcatact atgttatcac aagttccaag cagtttcaat
2751  acaaacatag gatatgttaa caacttttga taagaatcaa gttaccaact
2801  gttcattgtg agctttgagc tgtatagaag gacaatgtat cccatacctc
2851  aatctttaat agtcatcagt cactggtccc gcaccaattt tttcgattcg
2901  catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaatata
2951  ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat
3001  aaatgtattt tttgtgg
```

Fig. 11B-2

```
   1  gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
  51  ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gaatttaaac caataatcac attggacacg aaaccacctc
 301  gtgatgccaa caagtcattg gcattcaatg gcgggttgaa gctaatcact
 351  ccgaaaactg aagttcccga cgagcacaca ccgatgatgt caccagtgaa
 401  tacaactaca aagattctac aacggagtgg tattaaaatg gaaatcccgc
 451  catatttgga tccagacagt caggatgatg acccggaaga tggtgtcaac
 501  tacccggatc cagatttatt tgacacaaaa aacacaaata tgaccgagta
 551  cgatttggat gtgttgaagc ttggaaaacc agcagtagat gaagcacgga
 601  aaaagatcga agttcccgac gctagtgcgc cgccaaacaa aattgtagaa
 651  tatttgatgt attatagaac gttaaaagaa agtgaactca tacaactgaa
 701  tgcgtatcgg acaaaacgaa atcgattatc gttgaacttg gtcaaaaaca
 751  atattgatcg agagttcgac caaaaagctt gcgagtccct ggtgaaaaaa
 801  ttgaaggata agaagaatga tctccagaac ctgattgatg tggttctttc
 851  aaaaggtaca aaatataccg gttgcattac aattccaagg acacttgatg
 901  gccggttaca ggtccacgga agaaaaggtt tccctcacgt agtctatggc
 951  aaactgtgga ggtttaatga aatgacaaaa aacgaaacgc gtcatgtgga
1001  ccactgcaag cacgcatttg aaatgaaaag tgacatggta tgcgtgaatc
1051  cctatcacta cgaaattgtc attggaacta tgattgttgg gcagagggat
1101  catgacaatc gagatatgcc gccgccacat caacgctacc acactccagg
1151  tcggcaggat ccagttgacg atatgagtag atttatacca ccagcttcca
1201  ttcgtccgcc tccgatgaac atgcacacaa ggcctcagcc tatgcctcaa
1251  caattgcctt cagttggcgc aacgtttgcc catcctctcc cacatcaggc
1301  gccacataac ccaggggttt cacatccgta ctccattgct ccacagaccc
1351  attacccgtt gaacatgaac ccaattccgc aaatgccgca aatgccacaa
1401  atgccaccac ctctccatca gggatatgga atgaatgggc cgagttgctc
1451  ttcagaaaac aacaatccat tccaccaaaa tcaccattat aatgatatta
1501  gccatccaaa tcactattcc tacgactgtg gtccgaactt gtacgggttt
1551  ccaactcctt atccggattt tcaccatcct ttcaatcagc aaccacacca
1601  gccgccacaa ctatcacaaa accatacgtc ccaacaaggc agtcatcaac
1651  cagggcacca aggtcaggta ccgaatgatc caccaatttc aagaccagtg
1701  ttacaaccat caacagtcac cttggacgtg ttccgtcggt actgtagaca
1751  gacatttgga aatcgatttt ttgaaggaga aagtgaacaa tccggcgcaa
1801  taattcggtc tagtaacaaa ttcattgaag aatttgattc gccgatttgt
1851  ggtgtgacag ttgttcgacc gcggatgaca gacggtgagg ttttggagaa
1901  catcatgccg gaagatgcac catatcatga catttgcaag ttcattttga
1951  ggctcacatc agaaagtgta actttctcag gagaggggcc agaagttagt
2001  gatttgaacg aaaaatgggg aacaattgtg tactatgaga aaaatttgca
2051  aattggcgag aaaaaatgtt cgagaggaaa tttccacgtg gatggcggat
```

Fig. 11C-1

```
2101  tcatttgctc tgagaatcgt tacagtctcg gacttgagcc aaatccaatt
2151  agagaaccag tggcgtttaa agttcgtaaa gcaatagtgg atggaattcg
2201  cttttcctac aaaaaagacg ggagtgtttg gcttcaaaac cgcatgaagt
2251  acccggtatt tgtcacttct gggtatctcg acgagcaatc aggaggccta
2301  aagaaggata aagtgcacaa agtttacgga tgtgcgtcta tcaaaacgtt
2351  tggcttcaac gtttccaaac aaatcatcag agacgcgctt ctttccaagc
2401  aaatggcaac aatgtacttg caaggaaaat tgactccgat gaattatatc
2451  tacgagaaga agactcagga agagctgcga agggaagcaa cacgcaccac
2501  tgattcattg gccaagtact gttgtgtccg tgtctcgttc tgcaaaggat
2551  ttggagaagc atacccagaa cgcccgtcaa ttcatgattg tccagtttgg
2601  attgagttga aaatcaacat tgcctacgat ttcatggatt caatctgcca
2651  gtacataacc aactgcttcg agccgctagg aatggaagat tttgcaaaat
2701  tgggaatcaa cgtcagtgat gactaaatga taacttttt cactcaccct
2751  actagatact gatttagtct tattccaaat catccaacga tatcaaactt
2801  tttcctttga actttgcata ctatgttatc acaagttcca agcagtttca
2851  atacaaacat aggatatgtt aacaactttt gataagaatc aagttaccaa
2901  ctgttcattg tgagctttga gctgtataga aggacaatgt atcccatacc
2951  tcaatcttta atagtcatca gtcactggtc ccgcaccaat tttttcgatt
3001  cgcatatgtc atatattgca ccgtggccct ttttattgta acttttaata
3051  tattttcttc ccaacttgtg aatatgattg atgaaccacc attttgagta
3101  ataaatgtat tttttgtgg
```

Fig. 11C-2

```
  1  MKLIATSLLV PDEHTPMMSP VNTTTKILQR SGIKMEIPPY LDPDSQDDDP
 51  EDGVNYPDPD LFDTKNTNMT EYDLDVLKLG KPAVDEARKK IEVPDASAPP
101  NKIVEYLMYY RTLKESELIQ LNAYRTKRNR LSLNLVKNNI DREFDQKACE
151  SLVKKLKDKK NDLQNLIDVV LSKGTKYTGC ITIPRTLDGR LQVHGRKGFP
201  HVVYGKLWRF NEMTKNETRH VDHCKHAFEM KSDMVCVNPY HYEIVIGTMI
251  VGQRDHDNRD MPPPHQRYHT PGRQDPVDDM SRFIPPASIR PPPMNMHTRP
301  QPMPQQLPSV GATFAHPLPH QAPHNPGVSH PYSIAPQTHY PLNMNPIPQM
351  PQMPQMPPPL HQGYGMNGPS CSSENNNPFH QNHHYNDISH PNHYSYDCGP
401  NLYGFPTPYP DFHHPFNQQP HQPPQLSQNH TSQQGSHQPG HQGQVPNDPP
451  ISRPVLQPST VTLDVFRRYC RQTFGNRFFE GESEQSGAII RSSNKFIEEF
501  DSPICGVTVV RPRMTDGEVL ENIMPEDAPY HDICKFILRL TSESVTFSGE
551  GPEVSDLNEK WGTIVYYEKN LQIGEKKCSR GNFHVDGGFI CSENRYSLGL
601  EPNPIREPVA FKVRKAIVDG IRFSYKKDGS VWLQNRMKYP VFVTSGYLDE
651  QSGGLKKDKV HKVYGCASIK TFGFNVSKQI IRDALLSKQM ATMYLQGKLT
701  PMNYIYEKKT QEELRREATR TTDSLAKYCC VRVSFCKGFG EAYPERPSIH
751  DCPVWIELKI NIAYDFMDSI CQYITNCFEP LGMEDFAKLG INVSDD
```

Fig. 12A

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NVPDEHTPMM SPVNTTTKIL QRSGIKMEIP
101 PYLDPDSQDD DPEDGVNYPD PDLFDTKNTN MTEYDLDVLK LGKPAVDEAR
151 KKIEVPDASA PPNKIVEYLM YYRTLKESEL IQLNAYRTKR NRLSLNLVKN
201 NIDREFDQKA CESLVKKLKD KKNDLQNLID VVLSKGTKYT GCITIPRTLD
251 GRLQVHGRKG FPHVVYGKLW RFNEMTKNET RHVDHCKHAF EMKSDMVCVN
301 PYHYEIVIGT MIVGQRDHDN RDMPPPHQRY HTPGRQDPVD DMSRFIPPAS
351 IRPPPMNMHT RPQPMPQQLP SVGATFAHPL PHQAPHNPGV SHPYSIAPQT
401 HYPLNMNPIP QMPQMPQMPP PLHQGYGMNG PSCSSENNNP FHQNHHYNDI
451 SHPNHYSYDC GPNLYGFPTP YPDFHHPFNQ QPHQPPQLSQ NHTSQQGSHQ
501 PGHQGQVPND PPISRPVLQP STVTLDVFRR YCRQTFGNRF FEGESEQSGA
551 IIRSSNKFIE EFDSPICGVT VVRPRMTDGE VLENIMPEDA PYHDICKFIL
601 RLTSESVTFS GEGPEVSDLN EKWGTIVYYE KNLQIGEKKC SRGNFHVDGG
651 FICSENRYSL GLEPNPIREP VAFKVRKAIV DGIRFSYKKD GSVWLQNRMK
701 YPVFVTSGYL DEQSGGLKKD KVHKVYGCAS IKTFGFNVSK QIIRDALLSK
751 QMATMYLQGK LTPMNYIYEK KTQEELRREA TRTTDSLAKY CCVRVSFCKG
801 FGEAYPERPS IHDCPVWIEL KINIAYDFMD SICQYITNCF EPLGMEDFAK
851 LGINVSDD
```

Fig. 12B

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NEFKPIITLD TKPPRDANKS LAFNGGLKLI
101 TPKTEVPDEH TPMMSPVNTT TKILQRSGIK MEIPPYLDPD SQDDDPEDGV
151 NYPDPDLFDT KNTNMTEYDL DVLKLGKPAV DEARKKIEVP DASAPPNKIV
201 EYLMYYRTLK ESELIQLNAY RTKRNRLSLN LVKNNIDREF DQKACESLVK
251 KLKDKKNDLQ NLIDVVLSKG TKYTGCITIP RTLDGRLQVH GRKGFPHVVY
301 GKLWRFNEMT KNETRHVDHC KHAFEMKSDM VCVNPYHYEI VIGTMIVGQR
351 DHDNRDMPPP HQRYHTPGRQ DPVDDMSRFI PPASIRPPPM NMHTRPQPMP
401 QQLPSVGATF AHPLPHQAPH NPGVSHPYSI APQTHYPLNM NPIPQMPQMP
451 QMPPPLHQGY GMNGPSCSSE NNNPFHQNHH YNDISHPNHY SYDCGPNLYG
501 FPTPYPDFHH PFNQQPHQPP QLSQNHTSQQ GSHQPGHQGQ VPNDPPISRP
551 VLQPSTVTLD VFRRYCRQTF GNRFFEGESE QSGAIIRSSN KFIEEFDSPI
601 CGVTVVRPRM TDGEVLENIM PEDAPYHDIC KFILRLTSES VTFSGEGPEV
651 SDLNEKWGTI VYYEKNLQIG EKKCSRGNFH VDGGFICSEN RYSLGLEPNP
701 IREPVAFKVR KAIVDGIRFS YKKDGSVWLQ NRMKYPVFVT SGYLDEQSGG
751 LKKDKVHKVY GCASIKTFGF NVSKQIIRDA LLSKQMATMY LQGKLTPMNY
801 IYEKKTQEEL RREATRTTDS LAKYCCVRVS FCKGFGEAYP ERPSIHDCPV
851 WIELKINIAY DFMDSICQYI TNCFEPLGME DFAKLGINVS DD
```

Fig. 12C

tgatctttcaagccgaagcaatcaagacctcaaagccaatcaactctactcacttttcttcagaaccttaacttttttgtg
tcactttccccaaaaaccgttcaagctgctgccttcactctcatcccctcctcttactccttctttctcgtccgctacta
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gatgatgatcaatgcaaggagcatttgataacgttccatcatctttccgtccccgaactcaatcgaacctctcgattcct
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ggttccagcaattccaagtgatattgttgatagaactgatcaaatgcgtatcgatgcaactactcatagttggtggagtt
cagattaagcaggagtcgaagccgattaagacggaaccaattgctccaccaccatcataccacgagttgaacagtgtccg
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cctatggaaactatcaaaatggtggaataactccaatcaattggctatcaacatccaactcatctccactgcctggaatt
caatcgtgtggaattgtagctgcacagcatactgtcgcttcttcatcggctcttccaattgatttggaaaatctgacact
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Fig. 13A

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Fig. 13B

MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTPDDVMMNDDMEPIPRDR
CNTWPMRRPQLEPPLNSSPIIHEQIPEEDADLYGSNEQCGQLGGASSNGST
AMLHTPDGSNSHQTSFPSDFRMSESPDDTVSGKKTTTRRNAWGNMSYAELI
TTAIMASPEKRLTLAQVYEWMVQNVPYFRDKGDSNSSAGWKNSIRHNLSLH
SRFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
RGAKKRIKERALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPS
SFRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDR
TDQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLL
RNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVA
AQHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14A

MQQYIYQESSATIPHHHLNQHNNPYHPMHPHHQLPHMQQLPQPLLNLNMTT
LTSSGSSVASSIGGGAQCSPCASGSSTAATNSSQQQQTVGQMLAASVPCSS
SGMTLGMSLNLSQGGGPMPAKKKRCRKKPTDQLAQKKPNPWGEESYSDIIA
KALESAPDGRLKLNEIYQWFSDNIPYFGERSSPEEAAGWKNSIRHNLSLHS
RFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSRR
GAKKRIKERALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPSS
FRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDRT
DQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLLR
NPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVAA
QHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14B

```
   1 cggaagccat ggagctcgag atctgattgc tggacacgga cggaactccg acgtatctcg
  61 cagatgcatg ttaacatttt acatccacaa ctgcaaacga tggtcgagca gtggcaaatg
 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa
 181 ggtgtcgcag atatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg
 241 tggtttcttg caaatgtgcg aacatcgcta gaaatcaagc tatcagattt caaacatcaa
 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat
 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc
 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga
 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctcactggat
 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt
 601 acgaagaaaa cgtgcttgac acgtggactt gagggtacca gtcactacgc gttccccgaa
 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaatcaaa agtcaaggct
 721 gccaagctga gttatcagat gttttggaga aaacgtaaag cggaaatcaa tggagtttgc
 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt
 841 cacacgtttc tctacgaaat gcgaaaattg gatgtatacg ataccgatga tcctgcagat
 901 gaaggatggt ttcttcaatt ggctggacgt accacgtttg ttacaaatcc agatgtcaaa
 961 cttacgtctt atgatggtgt ccgttcggaa ctggaaagct atcgatgccc tggattcgtt
1021 gttcgccgac aatcactagt cctcaaagac tattgtcgcc caaaaccact ctacgaacca
1081 cattatgtga gagcacacga acgaaaactt gctctagacg tgctcagcgt gtctatagat
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1381 aaatggaata aggaaatgta cacttttgat ctatacatga aggatatgcc accatctgca
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1681 atgccgagtc aaggacaata cacatatctc gtcaagcacc gaagtacttg gacggaaact
1741 ttgaatatta tgggtgatga ctatgagtcg tgtatcagag atccaggata taagaagctt
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1921 gaactcgcat ttgtgtggac tgatcgtgag aacttttccg agctctatgt gatgcttgaa
1981 aaatggaaac cgccgagtgt ggcagccgcg ttgactttgc ttggaaaacg ttgcacggat
2041 cgtgtgattc gaaagtttgc agtggagaag ttgaatgagc agctgagccc ggtcacattc
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2341 atcacccgac aagttgacat ggttgatgag ctcacacgaa tcagcactct tgtcaaagga
2401 atgccaaaag atgttgctac gatgaaactg cgtgacgagc ttcgatcgat tagtcataaa
2461 atggaaaata tggattctcc actggatcct gtgtacaaac tgggtgaaat gataatcgac
2521 aaagccatcg tcctaggaag tgcaaaacgt ccgttaatgc ttcactggaa gaacaaaaat
2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt
2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca
```

Fig. 15-1

2701 aacattgatt gctgtttgaa cccgtacgca gttcttccaa tgggagaaat gattggaatt
2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg
2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc
2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag
2941 aagattgata atactcaagc catgaagaaa tattttgaaa gtgtcgatcg attcctatac
3001 tcgtgtgttg gatattcagt tgccacgtac ataatgggaa tcaaggatcg tcacagtgat
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3241 ttcaaaacgt tatgcgtcga agcctacgaa gtaatgtgga ataatcgaga tttgttcgtt
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3361 gatcatttga agaaaaccct cttctgcaat ggagaaagca aagaagaagc gagaaagttt
3421 ttcgctggaa tctacgaaga agccttcaat ggatcatggt ctaccaaaac gaattggctc
3481 ttccacgcag tcaaacacta ctga

Fig. 15-2

```
   1 RKPWSSRSDC WTRTELRRIS QMHVNILHPQ LQTMVEQWQM RERPSLETEN GKGSLLLENE
  61 GVADIITMCP FGEVISVVFP WFLANVRTSL EIKLSDFKHQ LFELIAPMKW GTYSVKPQDY
 121 VFRQLNNFGE IEVIFNDDQP LSKLELHGTF PMLFLYQPDG INRDKELMSD ISHCLGYSLD
 181 KLEESLDEEL RQFRASLWAR TKKTCLTRGL EGTSHYAFPE EQYLCVGESC PKDLESKVKA
 241 AKLSYQMFWR KRKAEINGVC EKMMKIQIEF NPNETPKSLL HTFLYEMRKL DVYDTDDPAD
 301 EGWFLQLAGR TTFVTNPDVK LTSYDGVRSE LESYRCPGFV VRRQSLVLKD YCRPKPLYEP
 361 HYVRAHERKL ALDVLSVSID STPKQSKNSD MVMTDFRPTA SLKQVSLWDL DANLMIRPVN
 421 ISGFDFPADV DMYVRIEFSV YVGTLTLASK STTKVNAQFA KWNKEMYTFD LYMKDMPPSA
 481 VLSIRVLYGK VKLKSEEFEV GWVNMSLTDW RDELRQGQFL FHLWAPEPTA NRSRIGENGA
 541 RIGTNAAVTI EISSYGGRVR MPSQGQYTYL VKHRSTWTET LNIMGDDYES CIRDPGYKKL
 601 QMLVKKHESG IVLEEDEQRH VWMWRRYIQK QEPDLLIVLS ELAFVWTDRE NFSELYVMLE
 661 KWKPPSVAAA LTLLGKRCTD RVIRKFAVEK LNEQLSPVTF HLFILPLIQA LKYEPRAQSE
 721 VGMMLLTRAL CDYRIGHRLF WLLRAEIARL RDCDLKSEEY RRISLLMEAY LRGNEEHIKI
 781 ITRQVDMVDE LTRISTLVKG MPKDVATMKL RDELRSISHK MENMDSPLDP VYKLGEMIID
 841 KAIVLGSAKR PLMLHWKNKN PKSDLHLPFC AMIFKNGDDL RQDMLVLQVL EVMDNIWKAA
 901 NIDCCLNPYA VLPMGEMIGI IEVVPNCKTI FEIQVGTGFM NTAVRSIDPS FMNKWIRKQC
 961 GIEDEKKKSK KDSTKNPIEK KIDNTQAMKK YFESVDRFLY SCVGYSVATY IMGIKDRHSD
1021 NLMLTEDGKY VHIDFGHILG HGKTKLGIQR DRQPFILTEH FMTVIRSGKS VDGNSHELQK
1081 FKTLCVEAYE VMWNNRDLFV SLFTLMLGME LPELSTKADL DHLKKTLFCN GESKEEARKF
1141 FAGIYEEAFN GSWSTKTNWL FHAVKHY
```

Fig. 16

CONVERGENT TGF-β AND INSULIN SIGNALING ACTIVATE GLUCOSE-BASED METABOLISM GENES

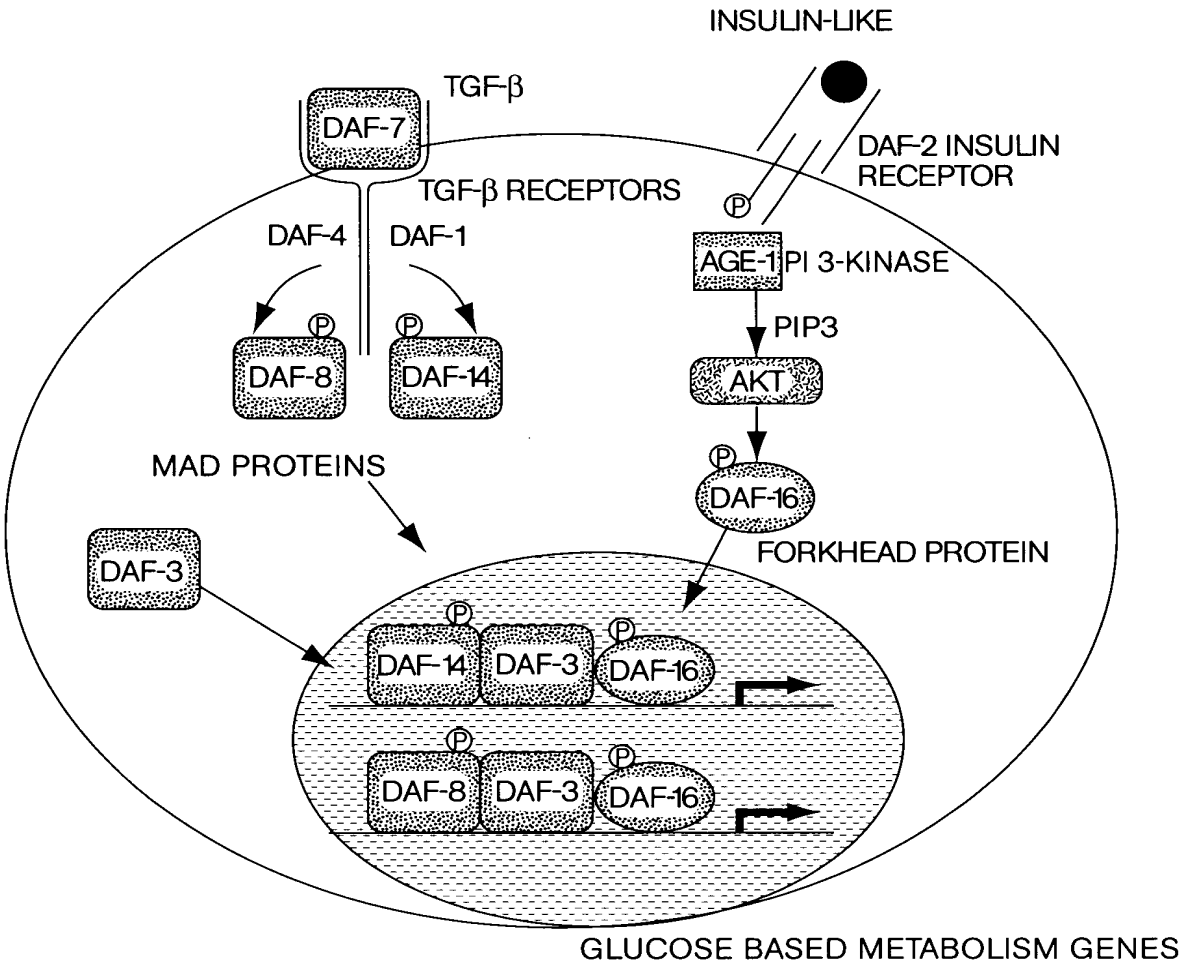


Fig. 17

IN PHEROMONE, NO TGFβ OR INSULIN-LIKE SIGNALS CAUSES REPRESSION OF ANABOLIC GENES

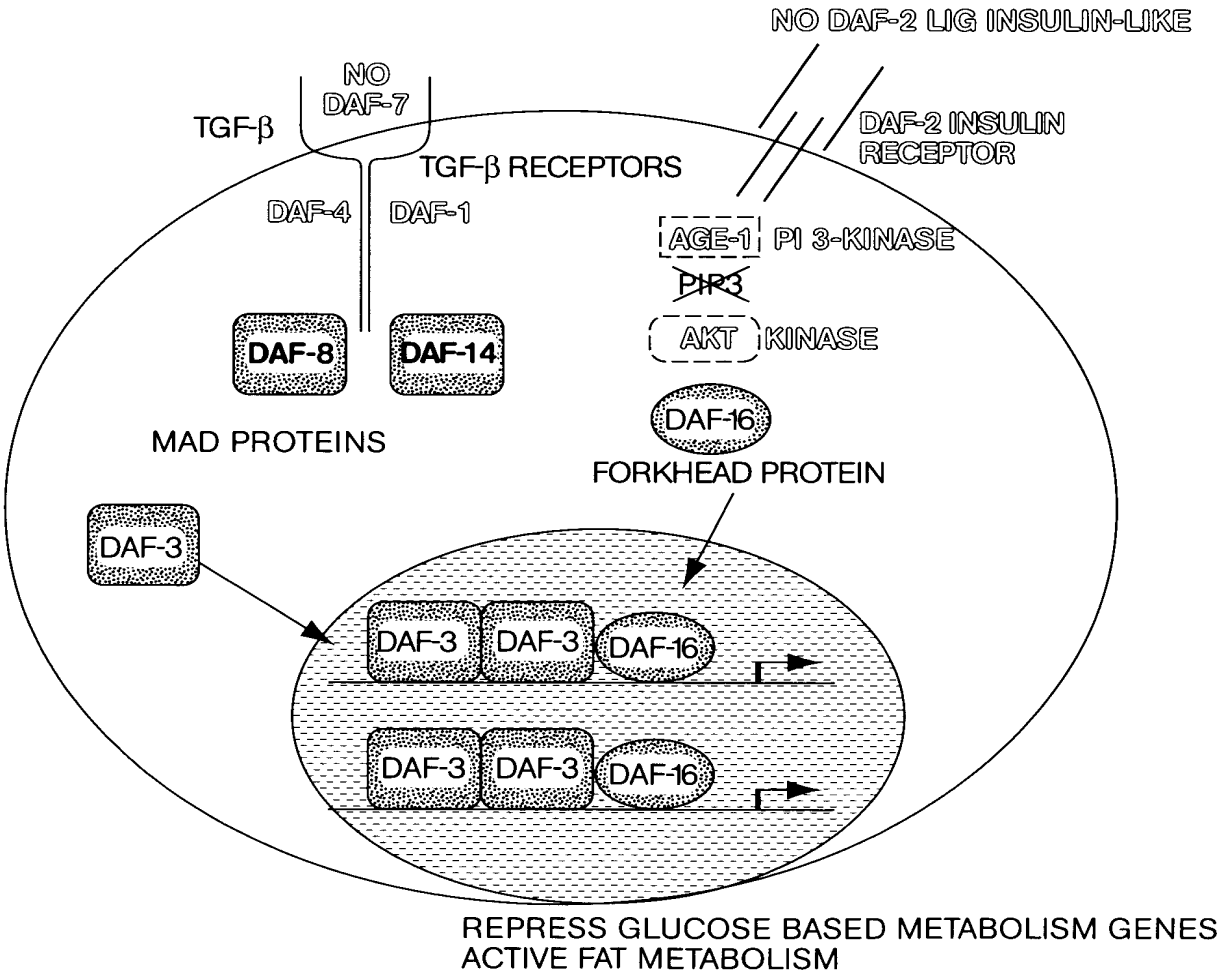
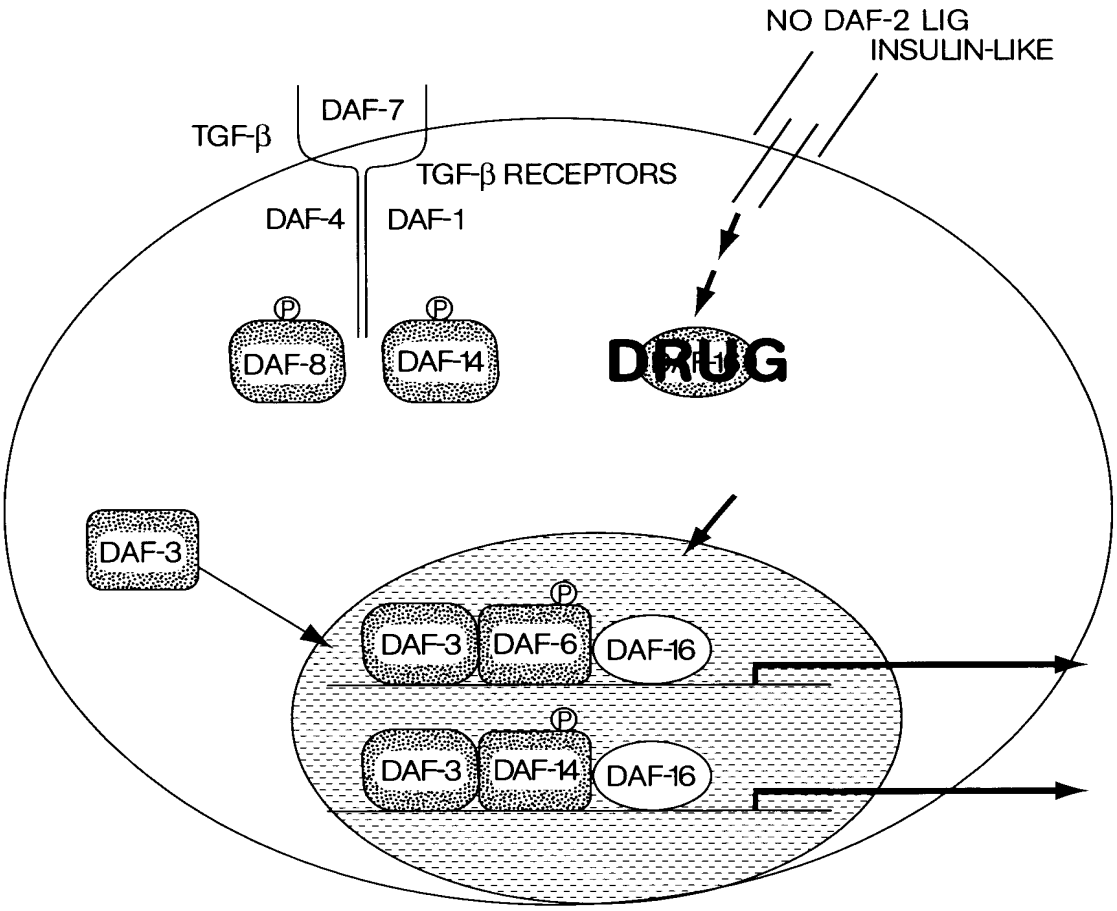


Fig. 18

**DRUGS THAT INHIBIT DAF-16 OR DAF-3
(OR PROTEINS IN THE PATHWAY)
CAN BE DISCOVERED USING REPORTER GENES
BEARING THEIR COGNATE BINDING SITES**



DRUG CAUSES A DECREASE IN DAF-16 ACTIVITY, ACTIVATING
THE REPORTER GENE LIKE A DAF-16 MUTANT.
THIS BYPASSES THE NEED FOR INSULIN

Fig. 19

DRUGS THAT INHIBIT DAF-3 WILL CURE THE DIABETES CAUSED BY A LACK OF DAF-7

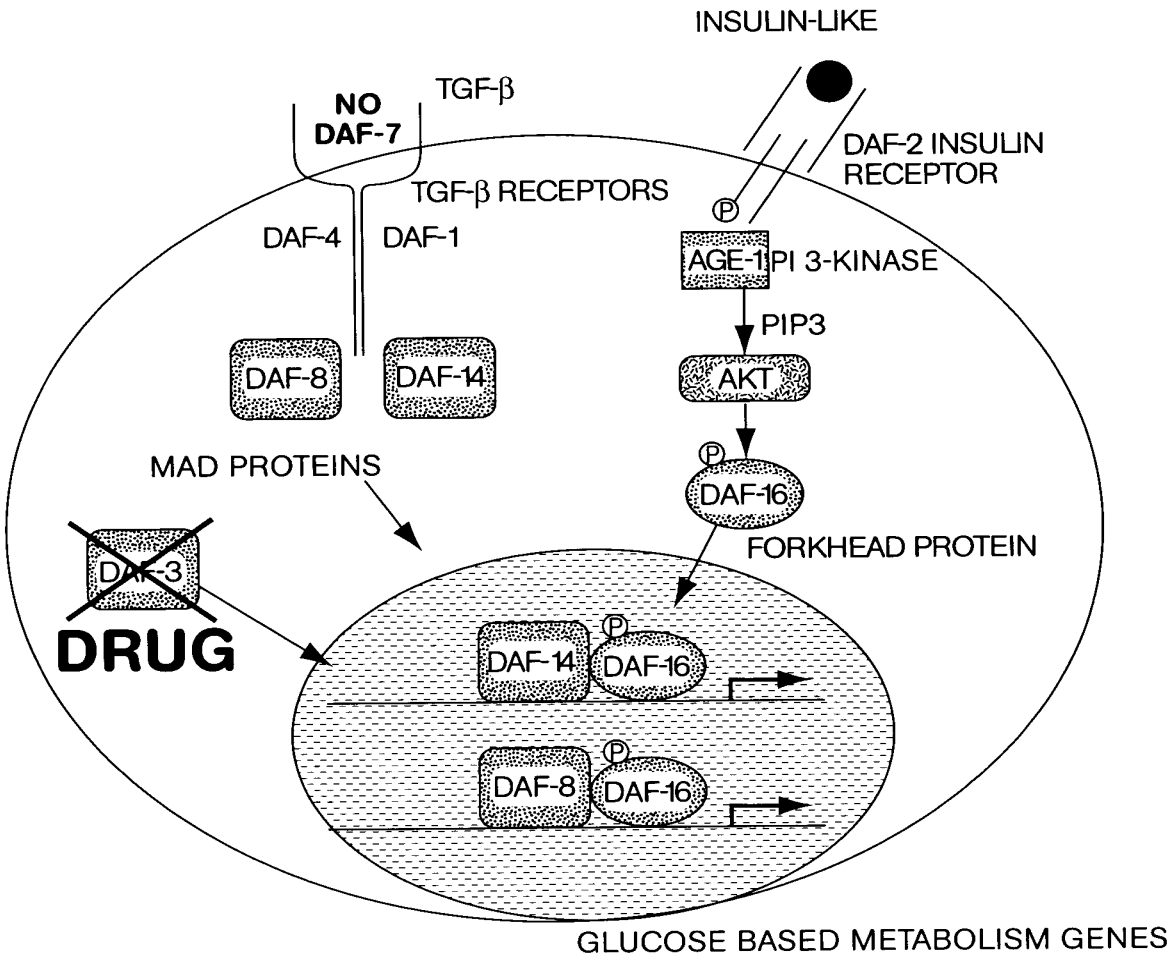


Fig. 20

Fig. 21A-1

```
DAF-16a1   511 ------------------------------------------------------------------------------
DAF-16b    531 ------------------------------------------------------------------------------
FKHR       511 ASHNKMMNPSSH.THPGHAQQTSAVNGRPLPHTVSTMPHTSGMNRLTQVKTPVQVPLPHPMQMSALGGYSSVSSCNGYGR
FKHRL1     523 PNQGSLVN.QNL.LHHQHQTQGALGGSRALSNSVSNM.GLSESSSLGSAKHQQQSPVSQSMQ.TLSDSLSGSSLYSTSAN
AFX        464 QDLDLDMYMENLECDMDNIISDLMDEGEGLDFNFEPDP----------------------------------------

DAF-16a1   511 ------------------------------------------------------------------------
DAF-16b    531 ------------------------------------------------------------------------
FKHR       590 MGLLHQEKLPSDLD.GMFIERLDCDMESIIRNDLMDGDILDFNFDNVLPNQ........SEPHSVKTTTHSWVSG
FKHRL1     599 LPVMGHEKFPSDLDLDMFNGSLECDMESIIRSELMDADGLDFNFDSLISTQNVVGLNVGNFTGAKQASSQSWVPG
AFX        502 ------------------------------------------------------------------------
```

Fig. 21A-2

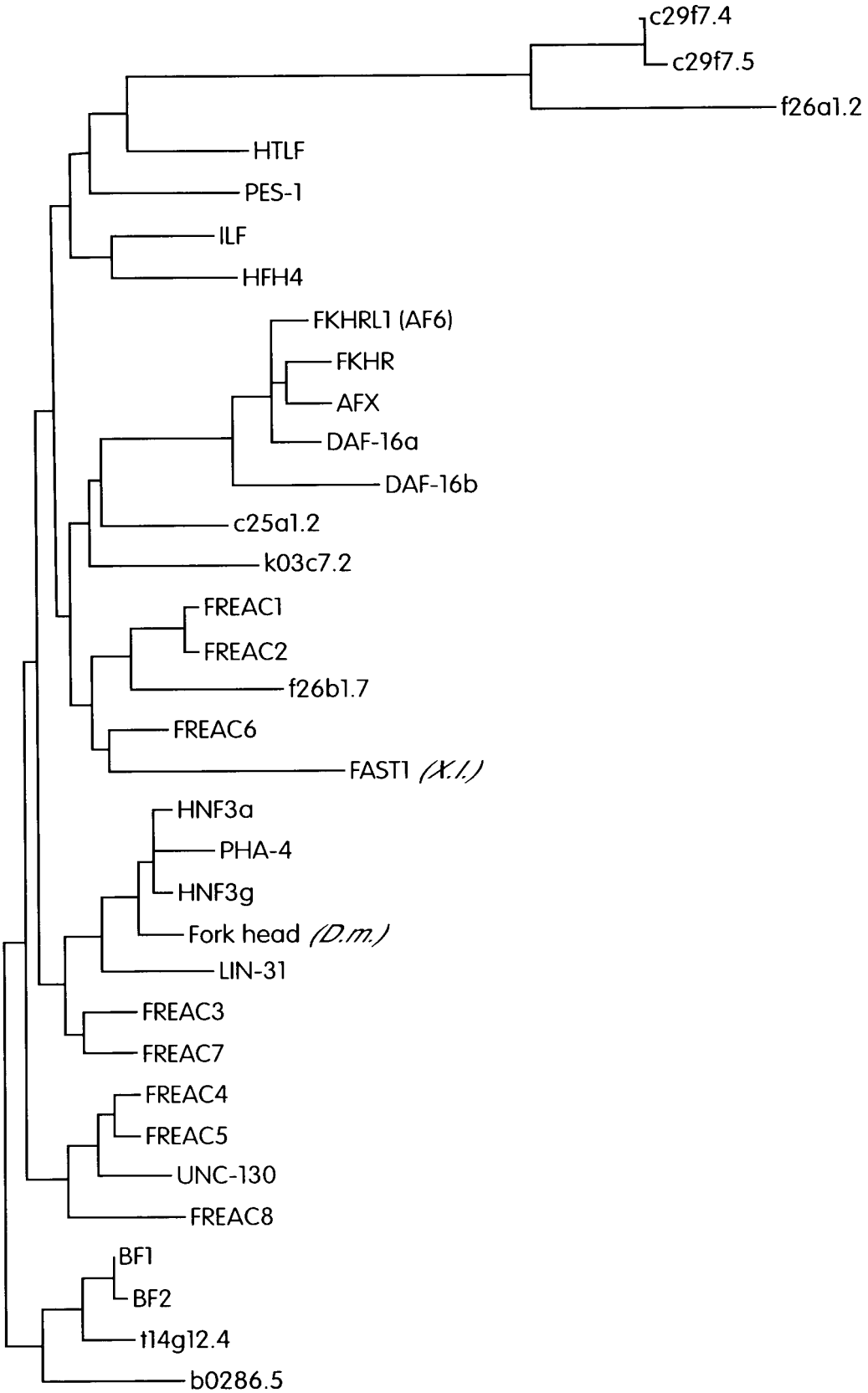


Fig. 21B

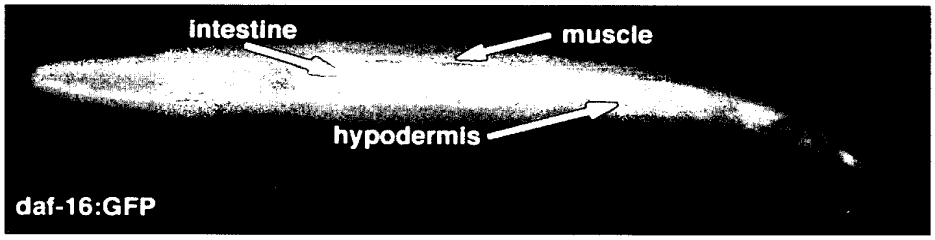
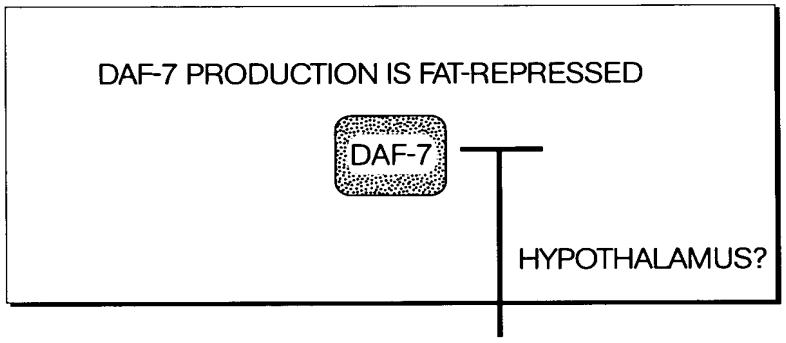


Fig. 22

INJECTION OF OF DAF-7 BYPASSES OBESITY-INDUCED DEFECTS IN INSULIN-REGULATION OF METABOLISM



FATTY ACIDS IN BLOOD REPRESS DAF-7 IN ANALOGY TO PHEROMONE REGULATION OF DAF-7 IN C. ELEGANS

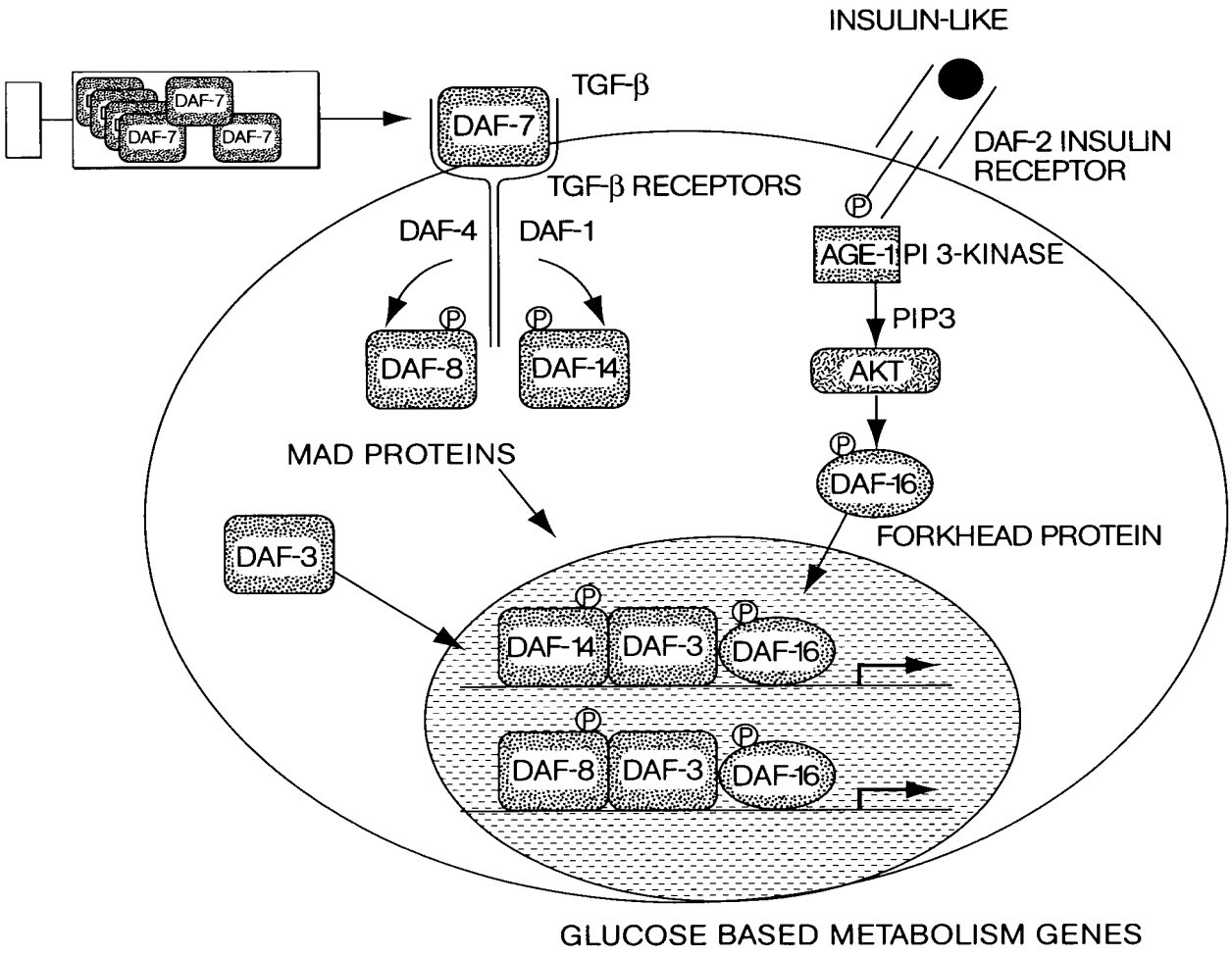


Fig. 23

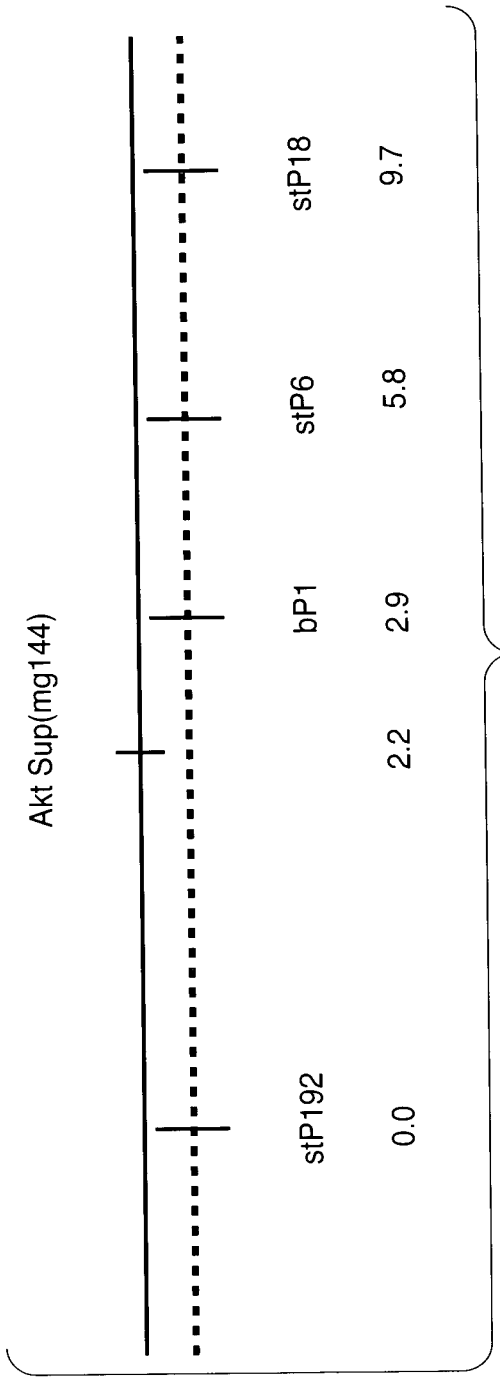


Fig. 24

Comparison of the human AKT protein sequence to the cosmid sequence C12D8, located in the genetic interval where sup(mg144) maps. Numbering in the AKT protein sequence by amino acid residues, and in the cosmid sequence by nucleotide position.

```
Score = 450 (207.4 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
Identities = 79/121 (65%), Positives = 97/121 (80%), Frame = +1

Query:    319 EVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILMEEIRFPRTLGPEAKS 378
              +VL+D+DYGR VDWWG+GVVMYEMMCGRLPFY++DH KLFELI+  ++RFP  L  EA++
Sbjct:  33685 QVLDDHDYGRCVDWWGVGVVMYEMMCGRLPFYSKDHNKLFELIMAGDLRFPSKLSQEART 33864

Query:    379 LLSGLLKKDPTQRLGGGSEDAKEIMQHRFFANIVWQDVYEKKLSPPFKPQVTSETDTRYFD 439
              LL+GLL KDPTQRLGGG EDA EI +  FF  + W+  Y K++ PP+KP V SETDT YFD
Sbjct:  33865 LLTGLLVKDPTQRLGGGPEDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFD 34047

 Score = 256 (118.0 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 48/66 (72%), Positives = 59/66 (89%), Frame = +1

Query:    146 TMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKILKKEVIVAKDEVAHTLTENRVLQNS 205
              TM +F++LK+LGKGTFGKVIL KEK T + YA+KILKK+VI+A++EVAHTLTENRVLQ
Sbjct:  32314 TMEDFDFLKVLGKGTFGKVILCKEKRTQKLYAIKILKKDVIIAREEVAHTLTENRVLQRC 32493

Query:    206 RHPFLT 211
              +HPFLT
Sbjct:  32494 KHPFLT 32511

 Score = 190 (87.6 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 36/45 (80%), Positives = 37/45 (82%), Frame = +2

Query:    276 KLENLMLDKDGHIKITDFGLCKEGIKDGATMKTFCGTPEYLAPEV 320
              KLENL+LDKDGHIKI DFGLCKE I  G    TFCGTPEYLAPEV
Sbjct:  33509 KLENLLLDKDGHIKIADFGLCKEEISFGDKTSTFCGTPEYLAPEV 33643

 Score = 188 (86.7 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 37/57 (64%), Positives = 42/57 (73%), Frame = +3

Query:    209 FLTALKYSFQTHDRLCFVMEYANGGELFFHLSRERVFSEDRARFYGAEIVSALDYLH 265
              +   LKYSFQ    LCFVM++ANGGELF H+ +   FSE RARFYGAEIV AL YLH
Sbjct:  32667 YFQELKYSFQEQHYLCFVMQFANGGELFTHVRKCGTFSEPRARFYGAEIVLALGYLH 32837

 Score = 166 (76.5 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 29/59 (49%), Positives = 42/59 (71%), Frame = +1

Query:     53 NNFSVAQCQLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREEWATAIQTVADGLK 111
              + F++   Q M  E+PRPN F++RCLQWTTVIERTF+ E+ E R+ W  AI++++   K
Sbjct:  31846 STFAIFYFQTMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESISKKYK 32022

 Score = 134 (61.8 bits), Expect = 5.2e-167, Sum P(8) = 5.2e-167
 Identities = 24/33 (72%), Positives = 30/33 (90%), Frame = +3

Query:    210 LTALKYSFQTHDRLCFVMEYANGGELFFHLSRE 242
              L  LKYSFQT+DRLCFVME+A GG+L++HL+RE
Sbjct:  33156 LQELKYSFQTNDRLCFVMEFAIGGDLYYHLNRE 33254
```

Fig. 25

Fig. 26A

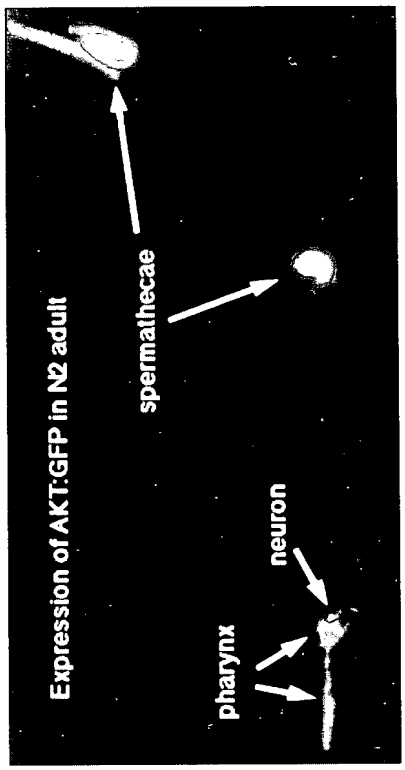


Fig. 26B

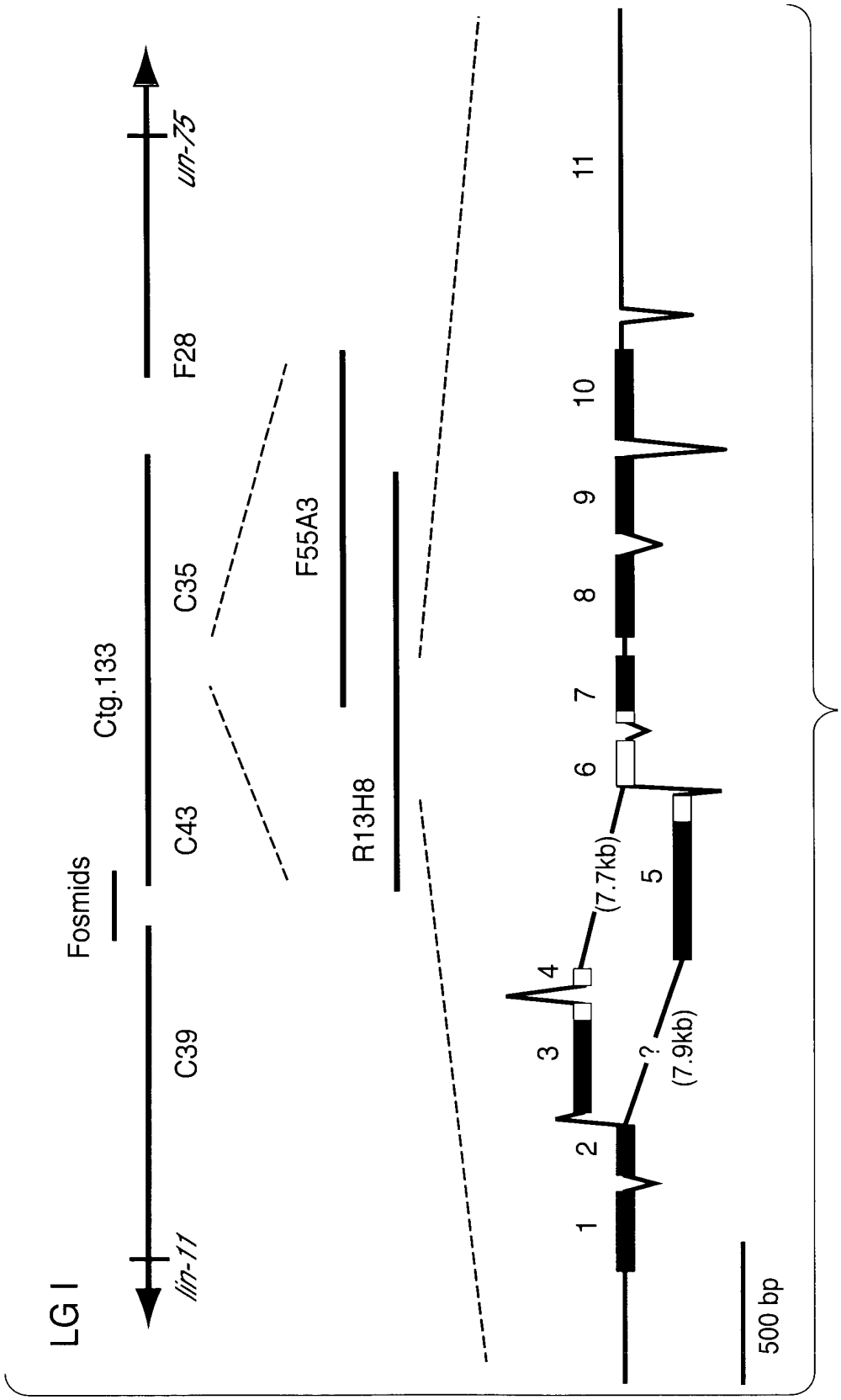


Fig. 27

```
                1               15 16              30 31              45 46              60
1 ZK84.6        -MNSVFTIIFVLCAL QVAASFRQSFG---P SMSEESASMQLLREL QH--NMMESAHRPMP  54
2 ZK75.1        -MFSFFT-YFLLSAL LLSASCRQ------P SMDT-SKADRILREI E----METELENQLS  47
3 ZK1251.2      ----MPPIILVFFLV LIPASQQY------P FSLE-SLNDQIINEE VI--EYMLENSIRSS  47
4 C06E2         --MIVTLIVFLVIGL QMAHLSQVSGNNENG FLNP-FDLSQWSEEI LHRQYHHHHHHHHGN  57
5 ZK75.2        ----MNAIIFCLLFT TVTATYEVF-----G KGIEHRNEHLIINQL D---IIPVESTPTPN  48
6 ZK75.3        MKLSVVLALFIIFQL GAASLMRN------W MFDFEKELEHDYDDS E---IGFHNIHSLMA  51
7 C17C3         --------------- --------------- ---------MKLLHI F---IIFLLFQSCSN  18
8 F13B12        --------------- --------------- ----MYWFRQVYRPS FF--FGFLAILLLSS  50
9 INSULIN       --------------- --------------- -------------MA LWMRLLPLLALLALW  17
CONSENSUS       --------------- --------------- --------------- ---------------

                61              75 76              90 91          105 106         120
1 ZK84.6        RARRVPAPGETRACG RKLISLVMAVCGD-L CN-------------- ---------------  85
2 ZK75.1        RARRVPA-GEVRACG RRLLLFVWSTCGE-P CT-------------- ---------------  77
3 ZK1251.2      RTRRVPDEKKIYRCG RRIHSYVFAVCGK-A CE-------------- ---------------  78
4 C06E2         RARRTLETEKIYRCG RKLYTDVLSACNG-P CE-------------- ---------------  88
5 ZK75.2        RASRVQK----RLCG RRLILFMLATCG--E CD-------------- ---------------  74
6 ZK75.3        RSRRGDK---VKICG TKVLKMVMVMCGG-E CS-------------- ---------------  79
7 C17C3         KMCQYSK-KKYKICG VRALKHMKVYCTR-G MT-------------- ---------------  48
8 F13B12         PTPSDAS---IRLCG SRLTTTLLAVCRNQL CTGLTAFKRSADQSY APTTRDLFHIHHQQ-  80
9 INSULIN       GPDPAAAFVNQHLCG SHLVEALYLVCGERG FFYTPKTRREAEDLQ VGQVELGGGPGAGSL  77
CONSENSUS       -------------CG -----------C---- ---------------- ---------------
                                        B CHAIN                    C PEPTIDE

                121             135 136             150 151         165 166         180
1 ZK84.6        -------PQEGKDIA TECCGNQCSDDYIRS ACCP-----    112
2 ZK75.1        -------PQEDMDIA TVCCTTQCTPSYIKQ ACCPEK---    106
3 ZK1251.2      -------SNTEVNIA SKCCREECTDDFIRK QCCP-----    105
4 C06E2         -------PGTEQDLS KLCCGNQCTFVEIRK ACCADKL--    118
5 ZK75.2        -------TDSSEDLS HICCIKQCDVQDIIR VCCPNSFRK    106
6 ZK75.3        -------S-TNENIA TECCEKMCTMEDITT KCCPSR---    107
7 C17C3         -------R-DYGKLL VTCCSKGCNAIDIQR ICL------     73
8 F13B12        ---------KRGGIA TECCEKRCSFAYLKT FCCNQDDN-     109
9 INSULIN       QPLALEGSLQKRGIV EQCCTSICSLYQLEN YCN-------    110
CONSENSUS       ----------------CC---C------- --C-------
                                  A CHAIN
```

Fig. 28

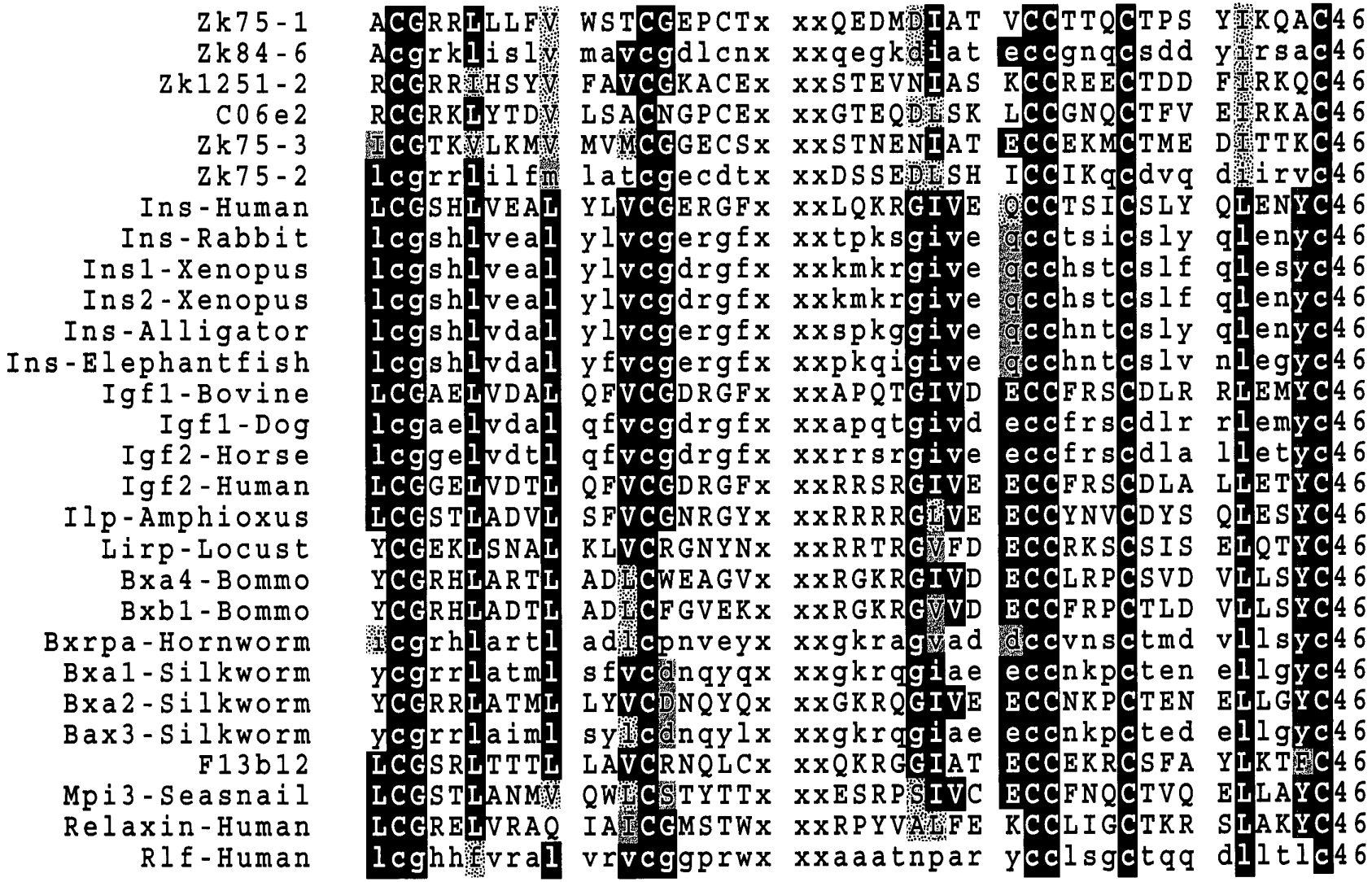


Fig. 29

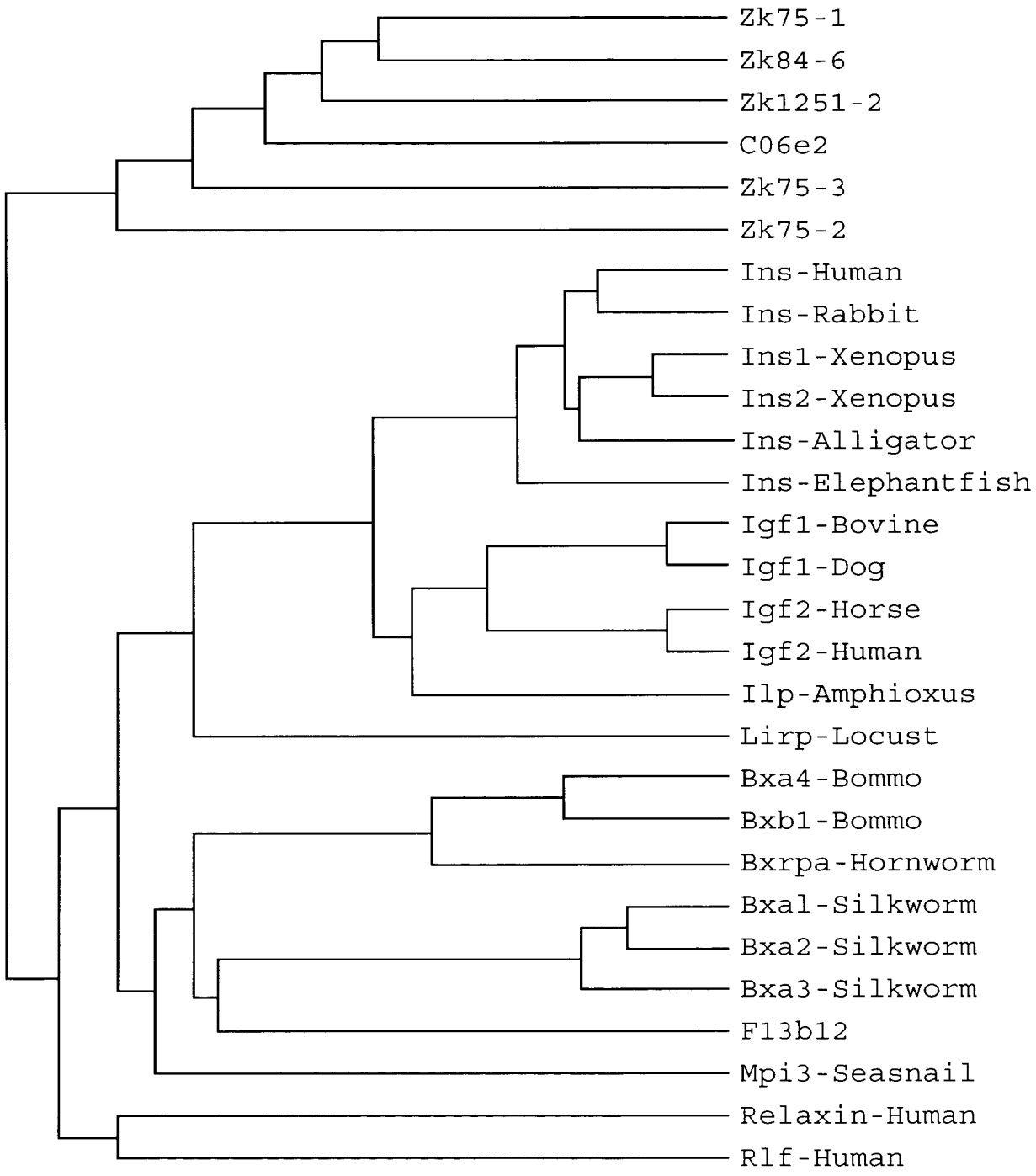


Fig. 30

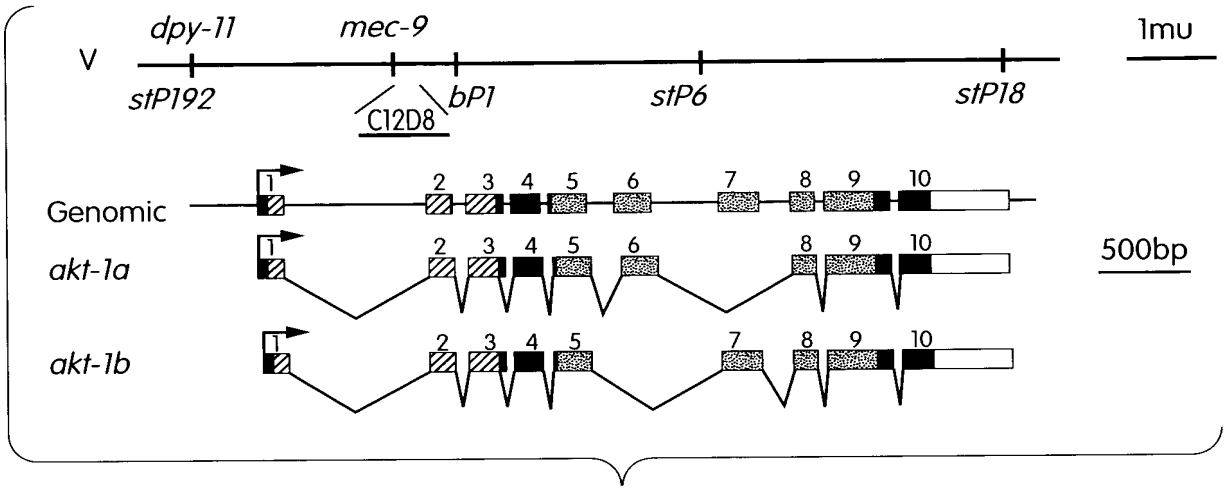


Fig. 31

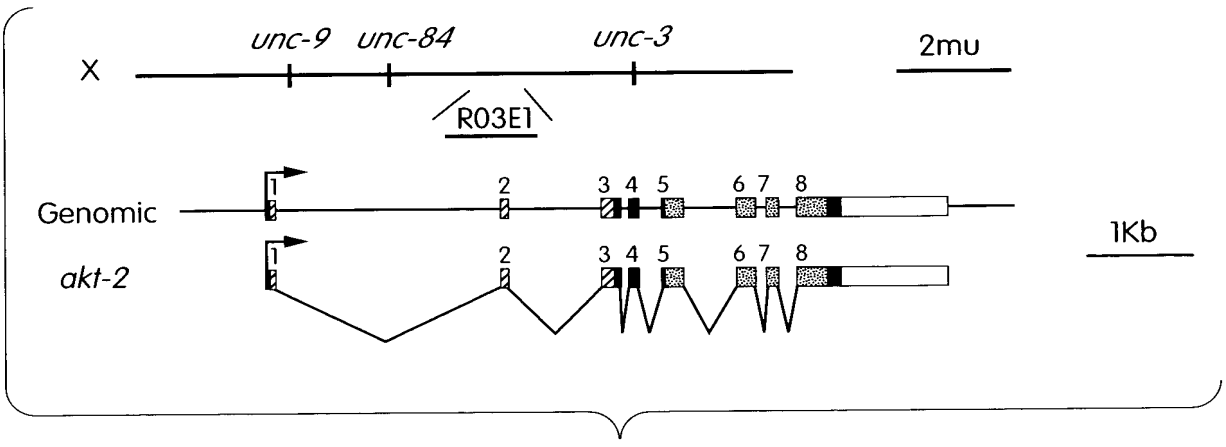


Fig. 32

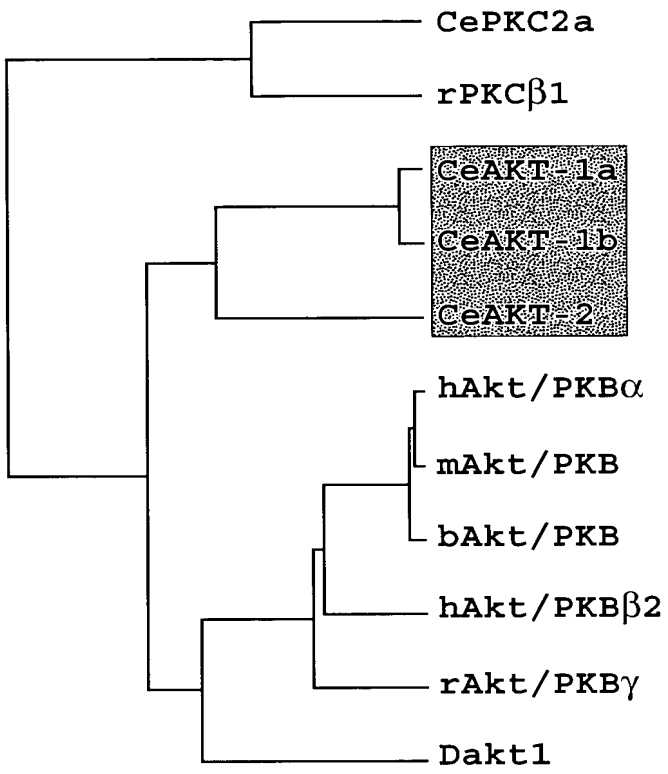


Fig. 33

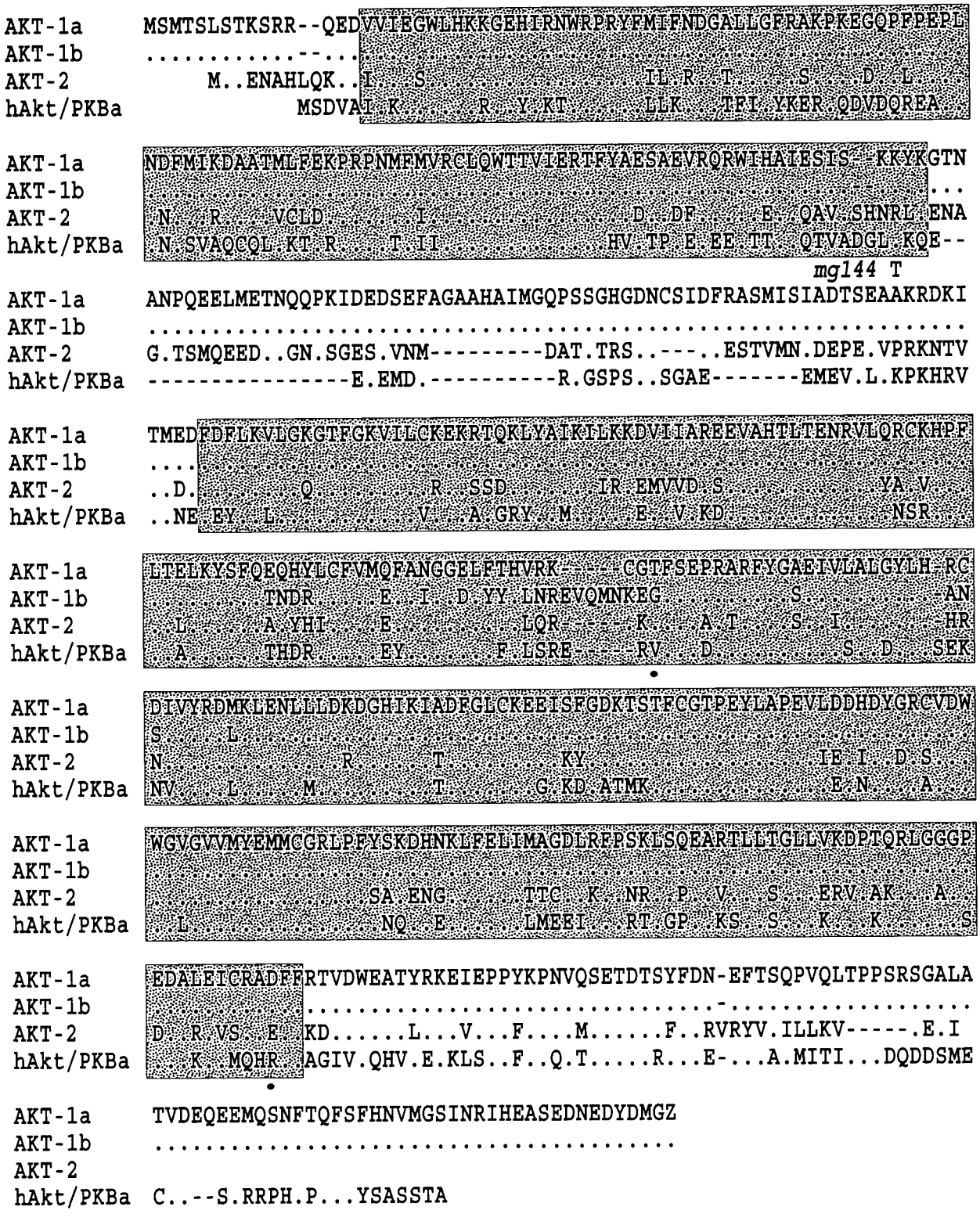


Fig. 34

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Fig. 35A

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agccggagtactactctaacattgggcctgtcgagccgggacttgatgatcGTGCCTTGTTCCGTTTGATGAATTTGGGAAATGATGCTAGCGCA
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TTGCGTCC

Fig. 35B

MEDLTPTNTSLDTTTTNNDTTSDREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
AYSQVFRCREVATDAMFAVKVLQKSYLNRHQKMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
DANQASSRSSDSGSPPPTRFYSDEEEENTARRTTFVGTALYVSPEMLADGDVGPQTDIWGLGCILFQCLAGQPPFRAV
NQYHLLKRIQELDFSFPEGFPEEASEIIAKILVRDPSTRITSQELMAHKFFENVDWVNIANIKPPVLHAYIPATFGEP
EYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEEQRVK
NPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIHTPNR
VYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEEKKAL
KAEQVSKKLSMQMDKKSP

Fig. 36

MEDLTPTNTSLDTTTTNNDTTSDREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
AYSQVFRCREVATDAMFAVKVLQKSYLNRHQKMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
DANQASSRSSDSGSPPPTRFYSDEEVPEENTARRTTFVGTALYVSPEMLADGDVGPQTDIWGLGCILFQCLAGQPPFR
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QRVKNPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIH
TPNRVYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEE
KKALKAEQVSKKLSMQMDKKSP

Fig. 37

Fig. 38A

Fig. 38B

Fig. 38C

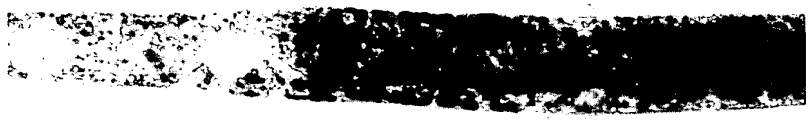

Fig. 38D

Fig. 38E

Fig. 38F

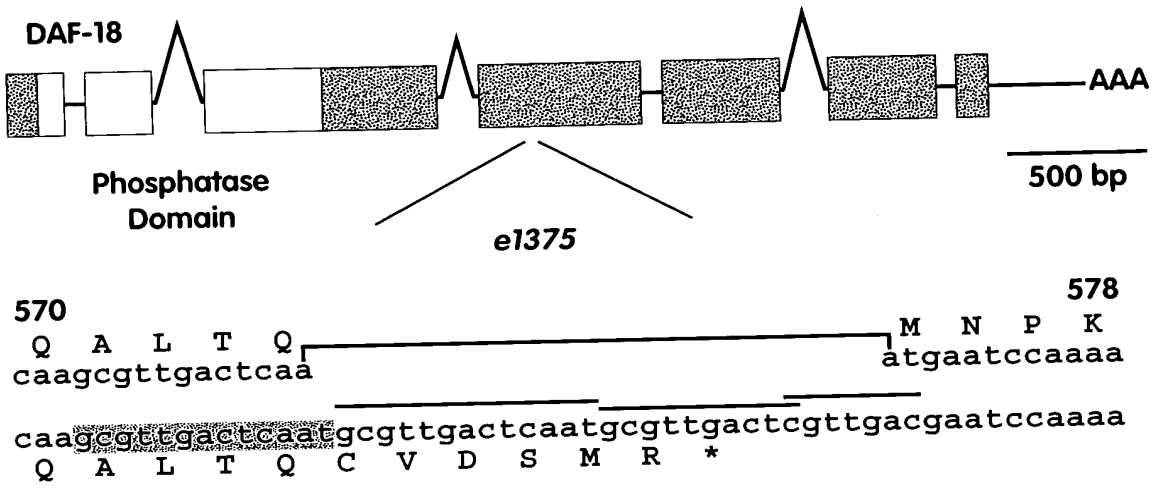

Fig. 39A

```
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PTEN      4 IIKEIVSRNK RRYQEDGFDL DLTYIYPNII AMGFPAERLE GVYRNNIDDV

DAF-18   98 QQFLTRRHGK GNVKVFNLRG GYYYDADNFD GNVICFDMTD HHPPSLELMA
PTEN     54 VRFLDSKH.K NHYKIYNLCA ERHYDTAKFN CRVAQYPFED HNPPQLELIK

DAF-18  148 PFCREAKEWL EADDKHVIAV HCKAGKGRTG VMICALLIYI NFYPSPRQIL
PTEN    103 PFCEDLDQWL SEDDNHVAAI HCKAGKGRTG VMICAYLLHR GKFLKAQEAL

DAF-18  198 DYYSIIRTKN NKGVTIPSQR RYIYYYHKLR ERELNYLPLR MQLIGVYVER
PTEN    153 DFYGEVRTRD KKGVTIPSQR RYVYYYSYLL KNHLDYRPVA LLFHKMMFET

DAF-18  248 PPKTWGGGSK IKVEVGNGST ILFKPD..PL IISKSNHQRE RATWLNNCDT
PTEN    203 IPMFSGGTCN PQFVVCQLKV KIYSSNSGPT RREDKFMYFE FPQPLPVCGD
```

Fig. 39B

DAF-18 Protein

MVTPPPDVPSTSTRSMARDLQENPNRQPGEPRVSEPYHNSIVERIRHIFRTAVSSNRCRTEYQNIDLDCAYITDRIIAIG
YPATGIEANFRNSKVQTQQFLTRRHGKGNVKVFNLRGGYYYDADNFDGNVICFDMTDHHPPSLELMAPFCREAKEWLEAD
DKHVIAVHCKAGKGRTGVMICALLIYINFYPSPRQILDYYSIIRTKNNKGVTIPSQRRYIYYYHKLRERELNYLPLRMQL
IGVYVERPPKTWGGGSKIKVEVGNGSTILFKPDPLIISKSNHQRERATWLNNCDTPNEFDTGEQKYHGFVSKRAYCFMVP
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YL

Fig. 40A

```
   1 ttccaggtac atctactaac ccccaatggt tactcctcct ccagatgtgc caagcacatc
  61 gaccaggtcg atggctcgtg accttcaaga gaatccaaac cgacaacctg gtgaaccacg
 121 tgtgtctgaa ccgtatcaca attcaatcgt cgagcggatt cgccatattt ttcggacggc
 181 tgtatcttcc aatcgttgtc gcaccgagta ccaaaatatc gacctagatt gtgcatatat
 241 cacagaccga atcatagcta tcggttatcc agcaacagga atcgaagcga atttccgtaa
 301 ctcaaaagtt caaactcaac aatttctgac caggcggcac ggaaagggca acgtgaaggt
 361 gtttaacctg cgcggtggat actactacga tgcggataac ttcgatggaa atgttatttg
 421 cttcgatatg actgatcatc atccgccgag tctcgaatta atggctccgt tttgcagaga
 481 ggctaaggaa tggcttgaag cagacgataa acatgtaata gctgtacact gtaaagctgg
 541 aaaaggccgt accggagtga tgatatgtgc tcttctcatc tacatcaact tctatccgag
 601 cccacgacaa attctcgact actactcaat aattcgtaca aaaaacaaca aaggtgtcac
 661 aattccatca caacgacgct acatttacta ctaccataag cttcgtgaac gtgagctcaa
 721 ctatttacca ttgagaatgc agttgattgg tgtctacgtg gaacggcctc caaagacatg
 781 gggtggtggt tcaaagataa aagtggaggt tggaaatggc tcgacaattt tatttaagcc
 841 ggatcctctc ataatctcca aatcaaatca tcagcgagag cgtgcgacgt ggctgaacaa
 901 ctgtgatacg cctaacgaat tcgacaccgg agagcaaaaa tatcatggat ttgtttccaa
 961 gagagcatac tgttttatgg tgccagaaga tgctccagta tttgtcgaag gagatgttcg
1021 tatagacatt cgcgaaatcg gatttctcaa aaagttttcg gacgggaaga ttggtcatgt
1081 ttggttcaat acaatgttcg catgtgatgg aggactcaac ggtggacatt tcgagtacgt
1141 agacaaaact cagccgtaca tcggagacga tacatcaatc ggacggaaaa atggaatgcg
1201 aagaaatgaa acgccgatgc gaaaaattga tccagaaact ggaaatgaat ttgagtctcc
1261 gtggcaaata gtgaatcctc ctggactgga aaaacatatt acggaggaac aagcaatgga
1321 aaattatacc aattatggca tgattcctcc tcgatacacg atcagcaaga ttcttcacga
1381 aaagcatgaa aaaggtatcg tcaaggatga ctataatgat cgtaagctgc caatgggaga
1441 caaatcatac acggaatcag gaaaaagtgg agatattcga ggagtcggtg gtccatttga
1501 gataccatat aaagctgagg aacatgttct cacatttcca gtttatgaaa tggatcgagc
1561 attgaagagt aaagatctta acaacggaat gaaacttcac gttgttcttc gttgtgtaga
1621 tactcgtgat tcaaaaatga tggaaaagag cgaagtgttc ggcaatctgg cattccataa
1681 tgaatcgaca cggaggcttc aagcgttgac tcaaatgaat ccaaaatggc gacctgaacc
1741 gtgtgcgttc ggatccaaag gtgctgaaat gcattaccct ccgtcggttc gatattcaag
1801 caatgatgga aagtataatg gagcctgcag tgagaacctt gttagcgatt ttttcgagca
1861 cagaaatatt gccgttctta atcgatattg ccgatatttc tacaagcaac gcagtacatc
1921 tcgaagccgt tatccaagaa aattcagata ctgtcctctg atcaagaaac atttctacat
1981 tccagctgat accgatgatg ttgatgaaaa tgggcaaccg ttcttccact caccagagca
2041 ttacattaaa gaacaggaaa aaatagacgc agagaaagca gctaaaggaa ttgaaaatac
2101 tggacccagt acttcaggat caagtgctcc cggaactatc aagaaaacgg aagcttcaca
2161 atccgacaag gtgaagccgg caactgaaga cgaacttcct cctgcgaggc taccggataa
2221 tgtgcgaaga tttccagtcg tcggcgttga tttcgaaaat ccggaagaag aatcgtgtga
2281 acacaaaacc gtagagtcaa tagctggttt tgaaccactc gaacatctat tccatgaatc
2341 ataccatcca aatacggccg gtaacatgct gcgtcaggat tatcacactg attcggaagt
2401 gaaaatagct gaacaagagg caaaagcctt cgttgaccag ttgcttaatg gacaaggtgt
2461 attacaagag tttatgaagc aattcaaagt accatcggac aattcctttg ctgattatgt
```

Fig. 40B-1

```
2521 aaccggacag gccgaagttt ttaaagcaca gattgcgtta ctggagcagt cggaggattt
2581 tcaacgagtt caagcgaatg cagaggaagt cgatcttgaa cacactcttg gtgaagcgtt
2641 tgagcgattc gggcacgttg tagaagaatc gaatggttct tctaaaaatc caaaagccct
2701 gaaaactcga gaacaaatgg tgaaagaaac tggcaaagac actcagaaga cccgcaatca
2761 tgtgcttcta catttggaag ctaatcatcg tgtgcaaatc gagcgtcgtg aaacgtgccc
2821 ggagctacat ccagaggata aaatcccaag aattgctcat ttttccgaaa acagcttctc
2881 ggattcgaat tttgatcaag ctatttattt gtaaacctaa aacaaaactt ttagaagatt
2941 ttcttcttac tgaccctcca attttcagat aatttcaatg ttttaagttt tctcttcaaa
3001 gtatcattca ctttctgtat agtgttttgt tttttaacaa actattgttc gattattttg
3061 tatattcata ttatagctct caacttcccg attttccacg tatatatgta tattttgccg
3121 ggtgaaaaat agcaattccc tatgaatgta tccccttcca tctgttttct tactcagaaa
3181 ttgtaattca cattgcgggt catcactaat cctatgggct ttaacacaat tctcccataa
3241 attaattgta cttaccaatt ttttgtttaa ttatttagat ttgtaacatt gaaattggtg
3301 ataa
```

Fig. 40B-2

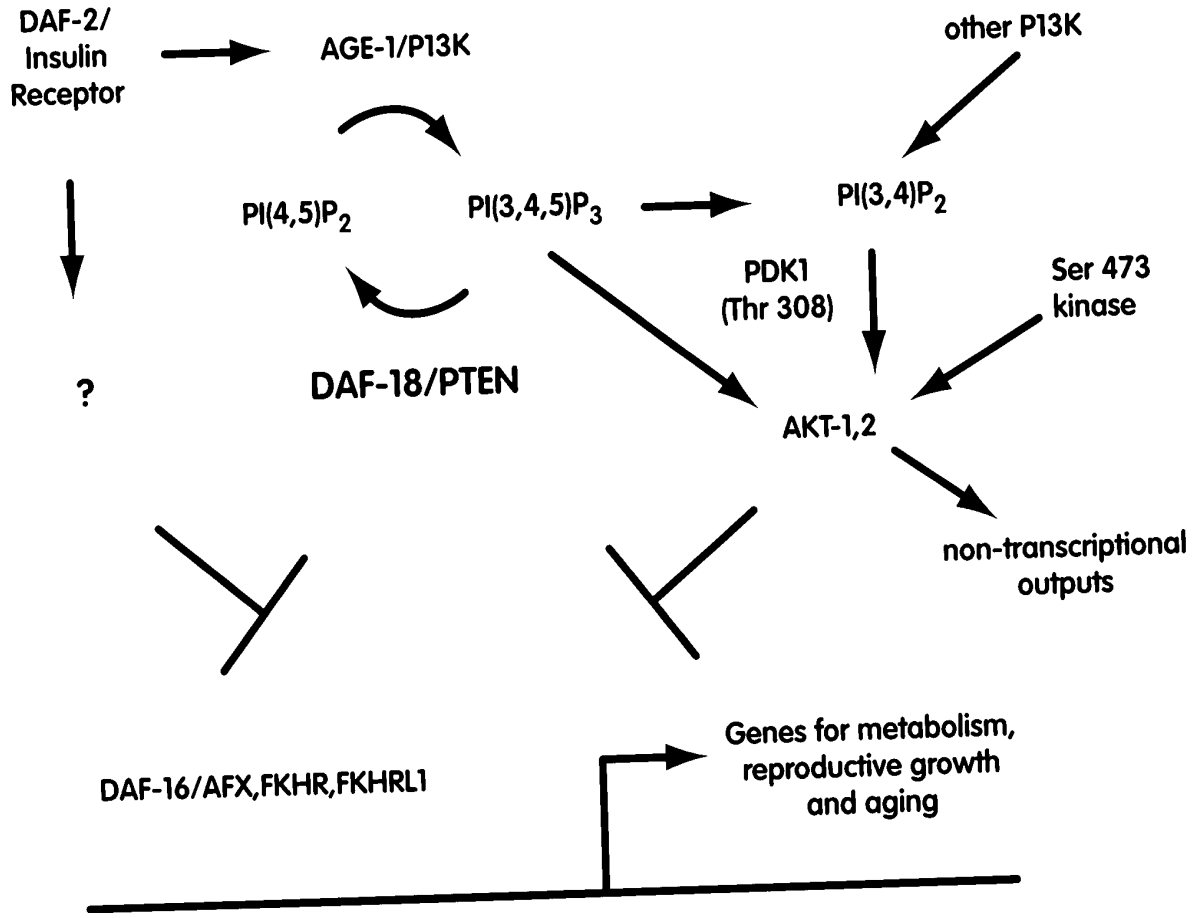

Fig. 41

```
                                                                                   ttta
attacccaagtttgaggtagcattgctctcttcaatcat atg gat tcg ttg ttt cag atg gca tcc gca
                                        M   D   S   L   F   Q   M   A   S   A

atg aag ttt caa tac tac tcg aag aaa gct gct gga aag aca atg tct aat agt gtc tcc
M   K   F   Q   Y   Y   S   K   K   A   A   G   K   T   M   S   N   S   V   S

atg tcc agt gac aat cgc atg gag gat ttt aaa cgt cgt ttt cgt cga agt gga tcg tta
M   S   S   D   N   R   M   E   D   F   K   R   R   F   R   R   S   G   S   L

gga att cca ttt gtc cca gaa gaa gat gtt aaa caa ctc ttc aca cca act cgt act gtt
G   I   P   F   V   P   E   E   D   V   K   Q   L   F   T   P   T   R   T   V

cgt cga gaa gca tst att cgc gaa ggg gat gag gaa gaa gga gta caa att ctc aca ata
R   R   E   A   S   I   R   E   G   D   E   E   E   G   V   R   I   L   T   I

att gtc aag tca agt cgt gtt tcg gag gat atc tca aaa atg att gca aac ctc cct gat
I   V   K   S   S   R   V   S   E   D   I   S   K   M   I   A   N   L   P   D

cac act cgt atc aaa cat ttg gag act cgt gac agt caa gat gga agt tcc aaa act atg
H   T   R   I   K   H   L   E   T   R   D   S   Q   D   G   S   S   K   T   M

gat gtt ctt cta gag att gag ctc ttt cat tat gga aaa caa gaa gca atg gat ctt atg
D   V   L   L   E   I   E   L   F   H   Y   G   K   Q   E   A   M   D   L   M

aga ctt aat ggg ctt gat gtt cat gag gtg tca tcg act att cgt cca act gca ata aaa
R   L   N   G   L   D   V   H   E   V   S   S   T   I   R   P   T   A   I   K

gag caa tat aca gag cct gga tct gat gat gcg aca acc ggt tct gaa tgg ttt cca aaa
E   Q   Y   T   E   P   G   S   D   D   A   T   T   G   S   E   W   F   P   K

agt att tat gat ttg gat att tgt gca aaa aga gtg att atg tat gga gca ggg ctg gac
S   I   Y   D   L   D   I   C   A   K   R   V   I   M   Y   G   A   G   L   D

gct gat cat cct ggt ttc aaa gat acc gag tat cgt caa cgt cga atg atg ttt gct gaa
A   D   H   P   G   F   K   D   T   E   Y   R   Q   R   R   M   M   F   A   E

ctg gcg ctc aat tac aaa cac ggt gag cca att ccg cga acc gaa tat aca tca tcc gaa
L   A   L   N   Y   K   H   G   E   P   I   P   R   T   E   Y   T   S   S   E

cgg aaa act tgg gga att ata tat aga aaa ttg aga gaa ttg cac aaa aag cac gca tgc
R   K   T   W   G   I   I   Y   R   K   L   R   E   L   H   K   K   H   A   C
```

Fig. 42-1

```
aag cag ttt ctt gat aac ttt gag cta ctg gag aga cat tgt gga tac tcg gaa aat aat
K   Q   F   L   D   N   F   E   L   L   E   R   H   C   G   Y   S   E   N   N

att ccg caa cta gaa gat atc tgc aag ttt ttg aaa gca aaa act gga ttc cgt gtt cgc
I   P   Q   L   E   D   I   C   K   F   L   K   A   K   T   G   F   R   V   R

cca gtc gcc gga tac tta tca gct cgt gat ttc ttg gca ggt ctt gca tat cgt gtc ttc
P   V   A   G   Y   L   S   A   R   D   F   L   A   G   L   A   Y   R   V   F

ttc tgc act caa tac gtt cgc cat cat gcc gat cca ttt tac act cca gaa cca gac acc
F   C   T   Q   Y   V   R   H   H   A   D   P   F   Y   T   P   E   P   D   T

gtt cac gag ctc atg ggt cac atg gct cta ttc gct gat cca gat ttt gct cag ttt tct
V   H   E   L   M   G   H   M   A   L   F   A   D   P   D   F   A   Q   F   S

caa gag att gga tta gct tct ctt gga gca tca gag gaa gat ttg aag aag ctt gca aca
Q   E   I   G   L   A   S   L   G   A   S   E   E   D   L   K   K   L   A   T

ctc tac ttc ttt tcc att gaa ttt ggt ctc tcg tct gat gac gct gcc gat tct cca gta
L   Y   F   F   S   I   E   F   G   L   S   S   D   D   A   A   D   S   P   V

aaa gaa aat gga tca aat cat gaa aga ttt aaa gta tac gga gca gga ctt ctg agc agt
K   E   N   G   S   N   H   E   R   F   K   V   Y   G   A   G   L   L   S   S

gct ggc gag ttg caa cat gcc gtt gag ggt agt gca acc att att cgt ttt gat ccg gat
A   G   E   L   Q   H   A   V   E   G   S   A   T   I   I   R   F   D   P   D

cgt gtt gtt gag caa gaa tgt ctc att act act ttc cag tca gcg tat ttc tat act aga
R   V   V   E   Q   E   C   L   I   T   T   F   Q   S   A   Y   F   Y   T   R

aat ttt gaa gag gcc cag cag aaa ctc aga atg ttc acc aac aac atg aaa cgt ccc ttc
N   F   E   E   A   Q   Q   K   L   R   M   F   T   N   N   M   K   R   P   F

att gtt cgt tac aac cca tac aca gaa agc gtc gaa gtt ctc aac aac tcc cgt tcc att
I   V   R   Y   N   P   Y   T   E   S   V   E   V   L   N   N   S   R   S   I

atg ttg gca gtg aac tct ctc cgc tca gac atc aac ctg ctc gcc gga gct ctc cac tac
M   L   A   V   N   S   L   R   S   D   I   N   L   L   A   G   A   L   H   Y

atc ctg tag
I   L   *
```

Fig. 42-2

```
                                                                  attacccaagtttgaggtagcattgctcttcttcaatcat

atg gat tcg ttg ttt cag atg gca tcc gca atg aag ttt caa tac tac tcg aag aaa gct
M   D   S   L   F   Q   M   A   S   A   M   K   F   Q   Y   Y   S   K   K   A

gct gga aag aca atg tct aat agt gtc aaa aac tgg att ccg tgt tcg ccc agt cgc cgg
A   G   K   T   M   S   N   S   V   K   N   W   I   P   C   S   P   S   R   R

ata ctt atc agc tcg tga ttt ctt ggc agg tct tgc ata tcg tgt ctt ctt ctg cac tca
I   L   I   S   S   *

ata cgt tcg cca tca tgc cga tcc att tta cac tcc aga acc aga cac cgt tca cga gct

cat ggg tca cat ggc tct att cgc tga tcc aga ttt tgc tca gtt ttc tca aga gat tgg

att agc ttc tct tgg agc atc aga gga aga ttt gaa gaa gct tgc aac act cta ctt ctt

ttc cat tga att tgg tct ctc gtc tga tga cgc tgc cga ttc tcc agt aaa aga aaa tgg

atc aaa tca tga aag att taa agt ata cgg agc agg act tct gag cag tgc tgg cga gtt

gca aca tgc cgt tga ggg tag tgc aac cat tat tcg ttt tga tcc gga tcg tgt tgt tga

gca aga atg tct cat tac tac ttt cca gtc agc gta ttt cta tac tag aaa ttt tga aga

ggc cca gca gaa act cag aat gtt cac caa caa cat gaa acg tcc ctt cat tgt tcg tta

caa ccc ata cac aga aag cgt cga agt tct caa caa ctc ccg ttc cat tat gtt ggc agt

gaa ctc tct ccg ctc aga cat caa cct gct cgc cgg agc tct cca cta cat cct gta g
```

Fig. 43

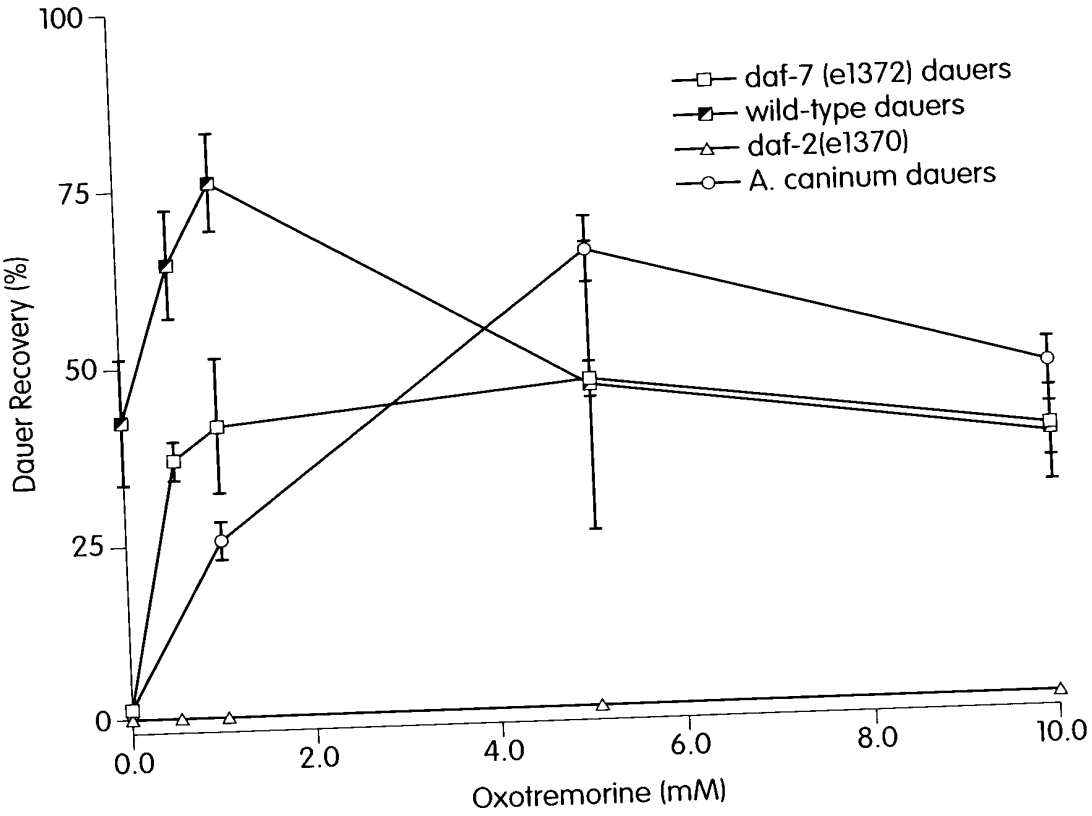

Fig. 44A

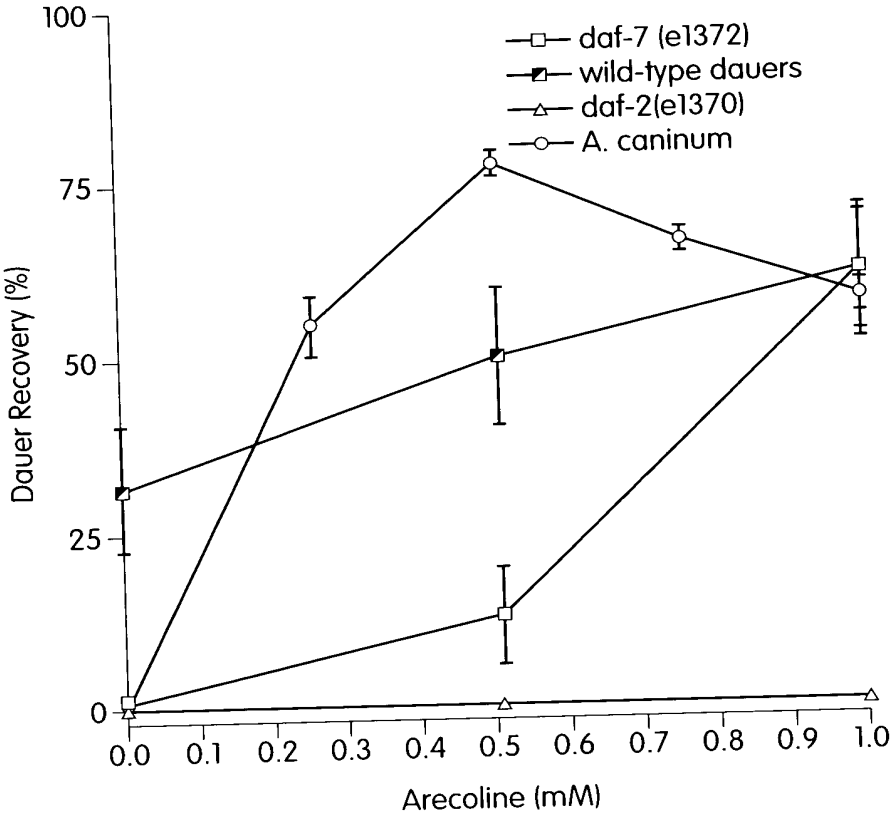

Fig. 44B

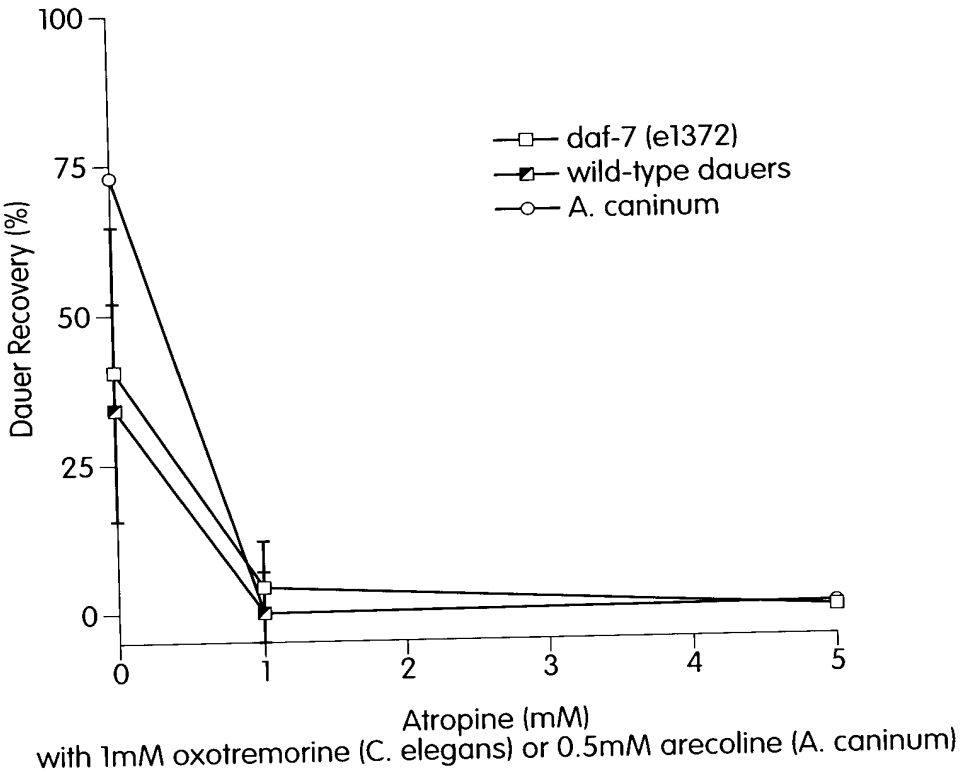

Fig. 44C

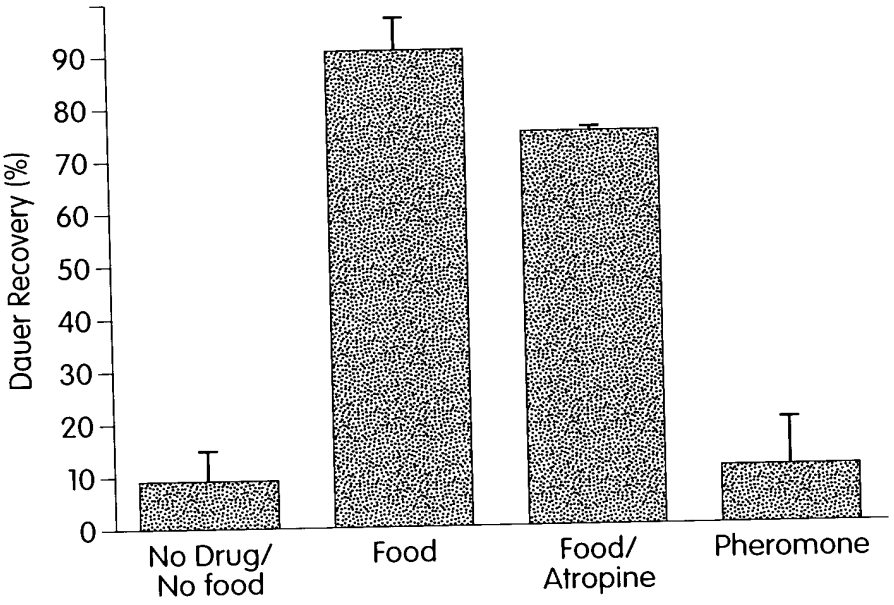

Fig. 45A

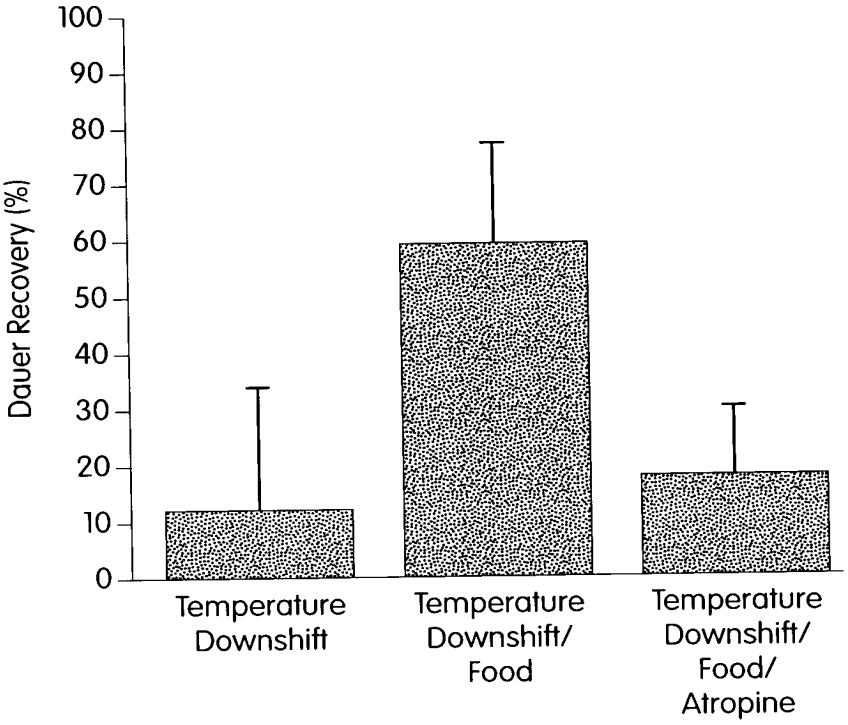

Fig. 45B

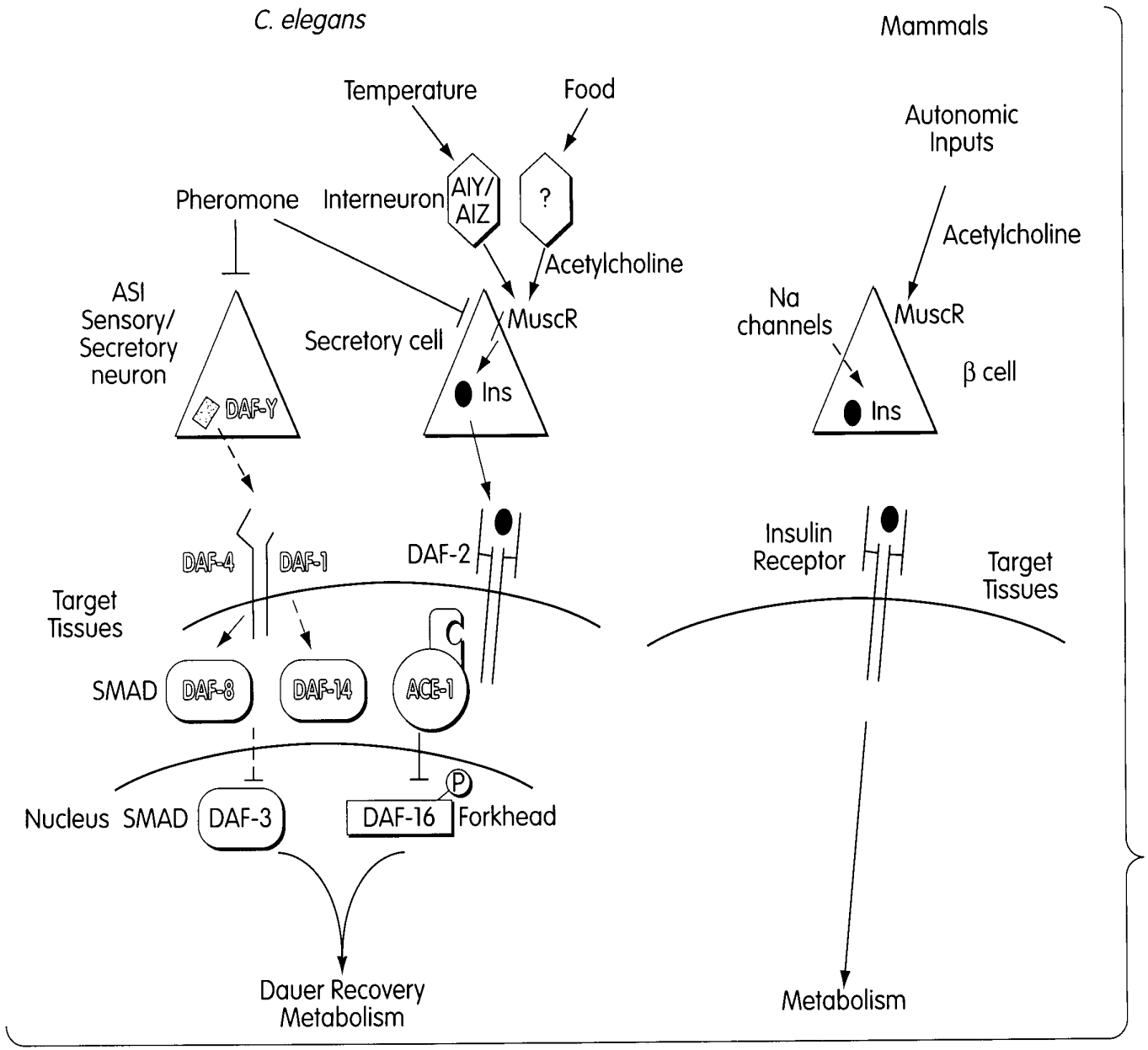

Fig. 46

```
ATTCGGCATGAGCATGGaGCTTCGAGTCCTAGAGAACACAAAACGTTCCCGGCGGAACCTGGGtCTGGACTGCGAC
GAGACTCAAGCGAGTCCCGCTGCTGCCGATATCCCCTCACAGTGGACTTTGAGGCTTTCGGCTGGGACTGGATCAT
CGCACCTAAGCGCTACAAGGCCAACTACTGCTCCGGCCAGTGGGAGTACATGTTCATGCAAAAATATCCGCATACC
CATTTGGTGCAGCAGGCCAATCCAAGAGGTTATGcTGGGCCCTGTTGTACCCCCACCAAGATGTCCCCAATcAACA
TgcTctACTTCAATGACAAGCAGCAGATTATcTACGGCAAGATCCCTGGCATGGTGGTGGATCGCTGTGGcTGCTC
TTAAGGTGGGGGGATAGAGGATGCCTCCCCCACAGACCGTACCCCAAGACCCATAGCCcTGCCCAATCCACCGCCTG
ATCCAAACAT
```

Fig. 47A


```
IRHEHGASSPREHKTFPAEPGSGLRRDSSESRCCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQWEYMFMQKYPHT
HLVQQANPRGYAGPCCTPTKMSPINMLYFNDKQQIIYGKIPLAMVVDRCGCS
```

Fig. 47B